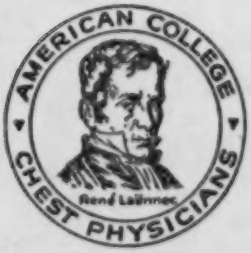
VOLUME XXXIV NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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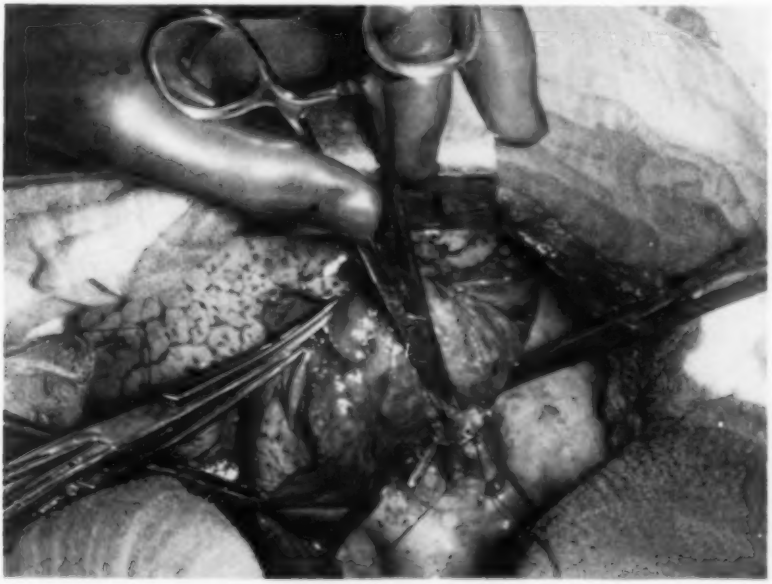

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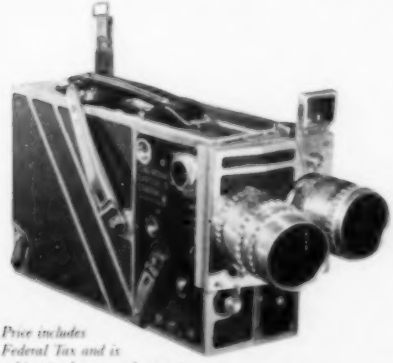

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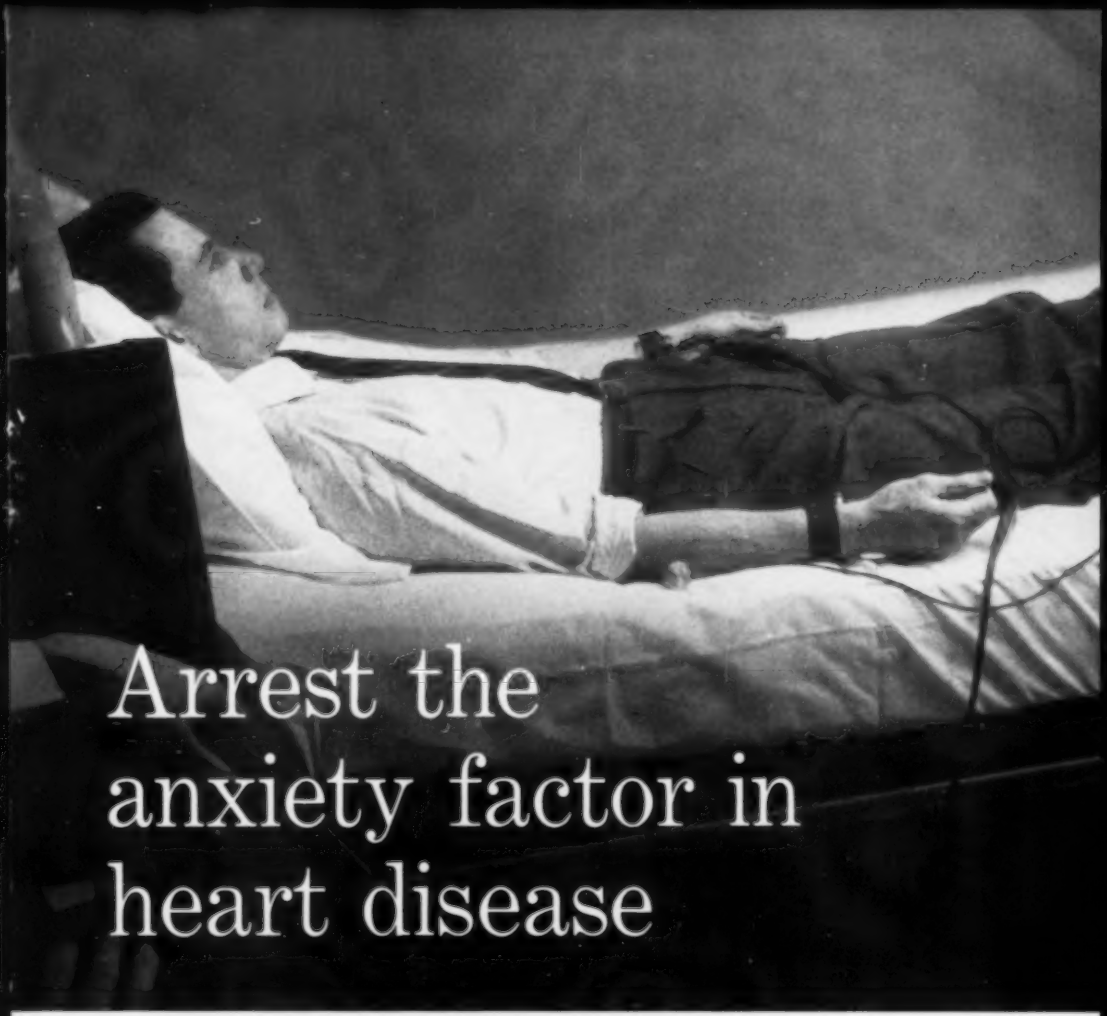

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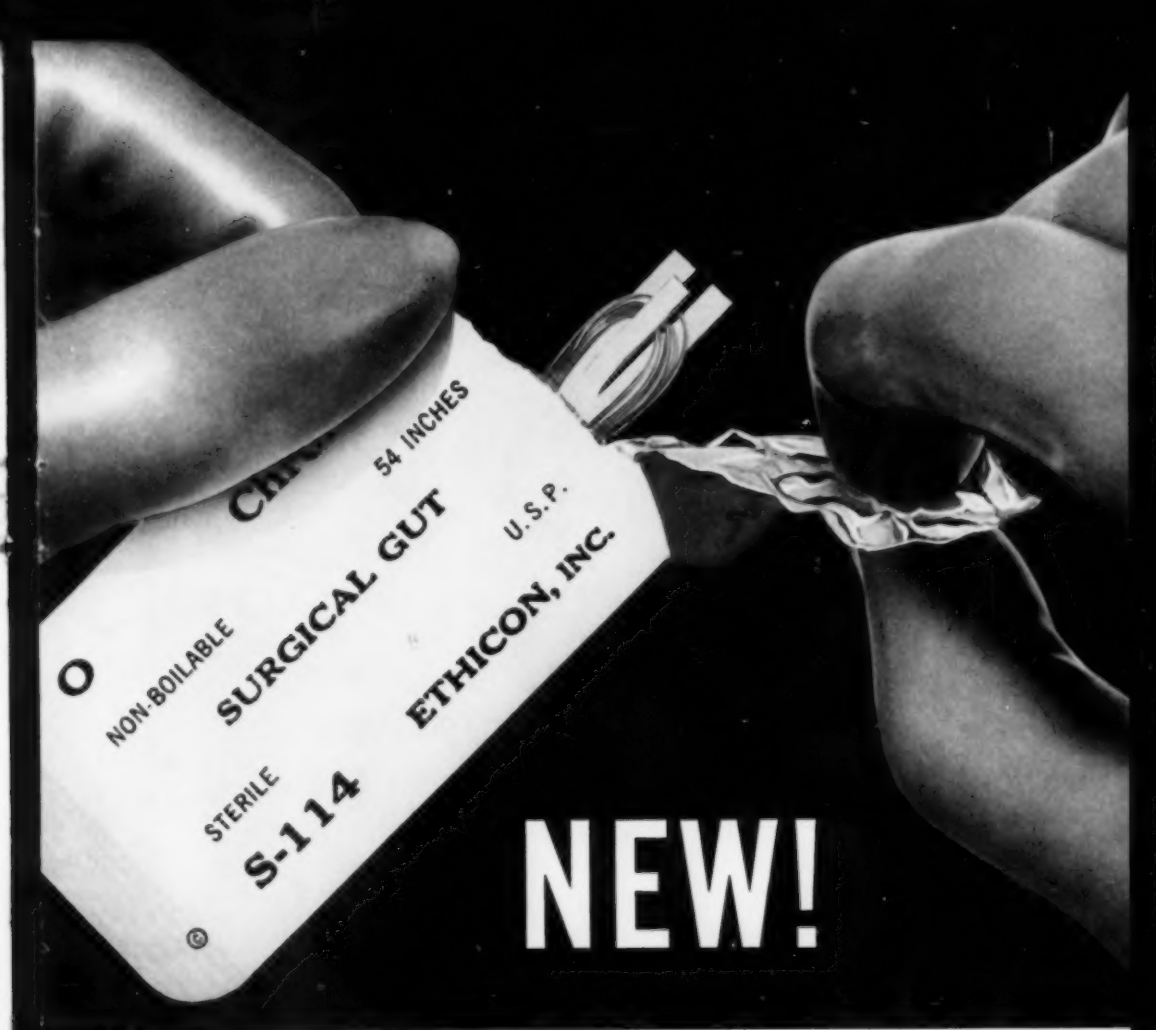

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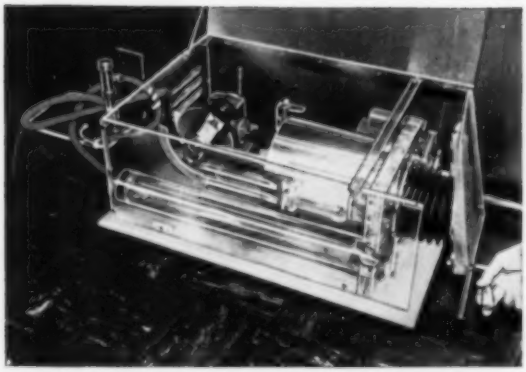

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1. Molthan, L., Cohen, R.V., and Zatafonetis, C.J.D.: Am. Rev. Tuber. *71*:220, 1955.
2. Cohen, R.V., Molthan, L., and Zatafonetis, C.J.D.: Dis. Chest *30*:418, 1956.

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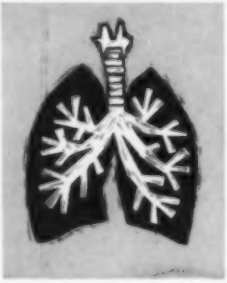

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1. Reports to the Squibb Institute of Medical Research, 1957. 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97, 1957. 3. Hellman, L., et al.: American Rheumatism Association. Interim session, Nov. 23, 1956. 4. Berntsen, C. A., Jr., et al.: New York Rheumatism Association. Annual meeting, April 9, 1957, New York. 5. Freyberg, R. H., et al.: International Congress on Rheumatic Diseases, June, 1957, Toronto.

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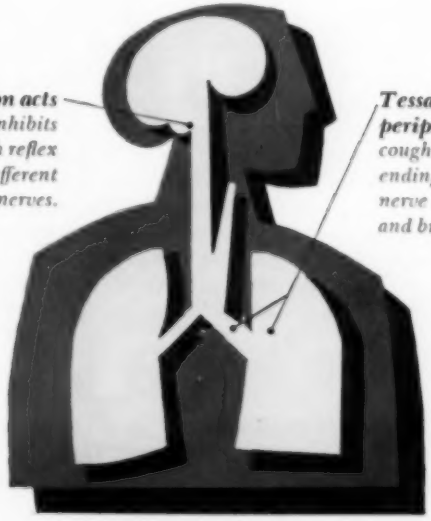

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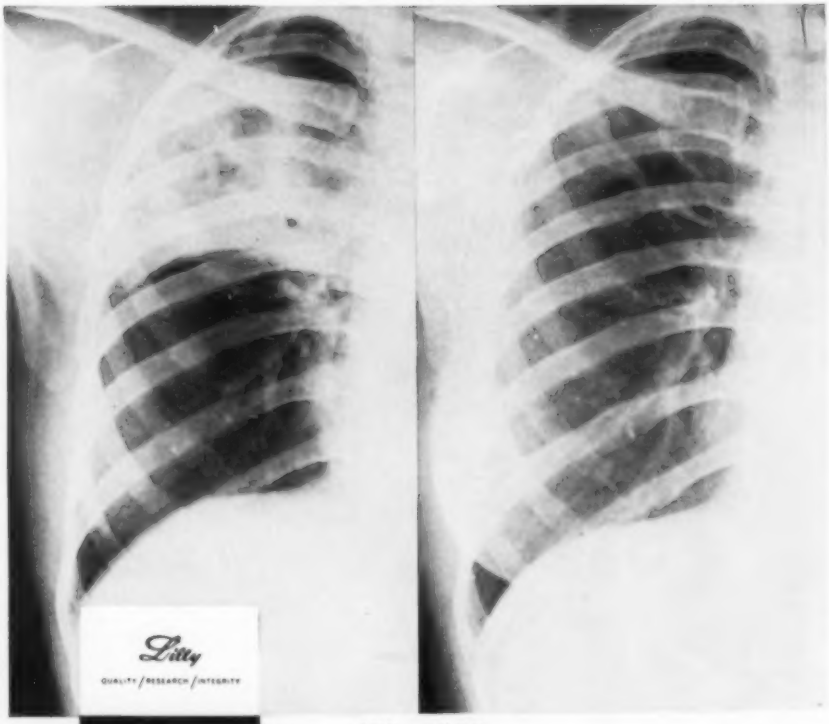

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DISEASES of the CHEST

VOLUME XXXIV JULY, 1958 NUMBER 1

Esophageal Disease as a Cause of Anterior Thoracic Pain*

HERMAN J. MOERSCH, M.D., F.C.C.P.**
and F. EDMUND DONOGHUE, M.D., F.C.C.P.**
Rochester, Minnesota

The occurrence of anterior thoracic pain in an individual past middle age is always a matter of alarm to the patient and of grave concern to the patient's attending physician. This is due to the fact that pain situated about the precordial region is associated in the minds of the laity and the medical profession with serious cardiac or pulmonary disease. That the esophagus may be responsible for the pain is seldom considered, and as a consequence the patient with anterior thoracic pain due to esophageal disease is often forced to undergo a long period of unnecessary invalidism before the true nature of the illness is recognized.

Because of the nature of the nerve supply of the esophagus, pain originating in the esophagus may have a bizarre distribution. The esophagus receives its nerve supply primarily from the vagus nerve and the sympathetic trunks. Visceral afferent impulses are carried to the central nervous system by way of the visceral rami of the sympathetic trunk. Sensation may be referred to the same or other somatic segments (fig. 1). Visceral afferent pain impulses may also be transmitted by way of the vagus nerve. Whether or not the phrenic nerve supplies the lower end of the esophagus has not been definitely established. It does, however, supply the central portion of the diaphragm through which the esophageal hiatus passes. Any disorder of the lower end of the esophagus that involves the esophageal hiatus will irritate afferent visceral pain endings of the phrenic nerve. The phrenic nerve, arising from the third to the fifth cervical roots, allows pain to be referred to the peripheral distribution of these roots. These roots supply the outer aspect of the appropriate shoulder and arm. It is obvious, then, that pain due to esophageal disturbance or disease may be referred to a considerable part of the thorax and neighboring structures.

*Read at the Interim Session of the American College of Chest Physicians, Boston, Massachusetts, November 27 and 28, 1955.

**Section of Medicine, Mayo Clinic and Mayo Foundation.
The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

What are some of the more common esophageal disorders that may produce anterior thoracic pain?

Esophageal Hiatal Hernia

Esophageal hiatal hernia is one of the most frequent causes of such pain. It is a disorder that may be very bizarre in its clinical manifestations, and it has aptly been termed "the great masquerader of the upper gastrointestinal tract." The importance of esophageal hiatal hernia as a diagnostic problem is clearly manifest when it is realized that approximately 8 per cent of the population of the United States are afflicted with this abnormality. This means that there are some 10,000,000 people in this country who have hiatal hernia.

Not all esophageal hiatal hernias cause symptoms. In our experience at the Mayo Clinic, approximately 25 per cent of the patients who have hiatal hernia are completely asymptomatic. In another 25 per cent, the symptoms have a very doubtful relationship to the hernia. In the remaining cases the hernia does produce symptoms.

One of the most common symptoms is pain. Pain occurs in approximately one third of the cases of hiatal hernia in which symptoms are produced. The pain varies greatly in its character, intensity, location

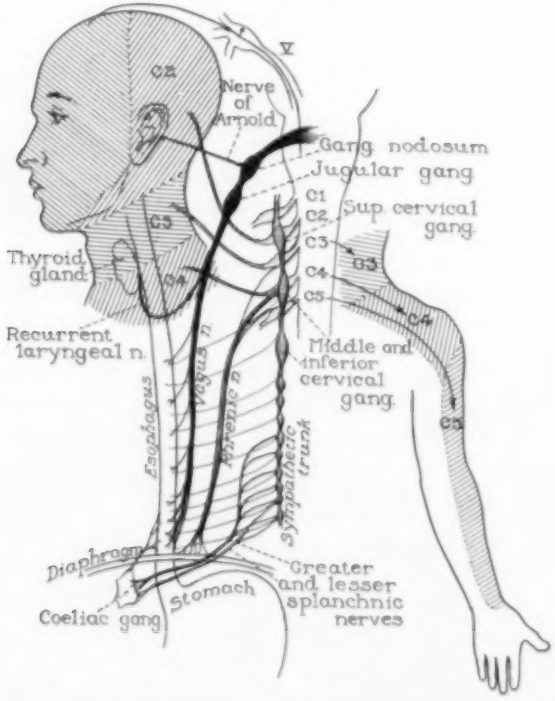

FIGURE 1: Nerve supply of esophagus.

and distribution. Most frequently it is located in the epigastric region, and tends to occur soon after eating. It is often aggravated when the patient assumes a recumbent position. The pain has a tendency to radiate out along the costal margins or straight through into the back. In approximately one out of ten patients with esophageal hernia that have pain, the pain is substernal. It may or may not be related to the ingestion of food and on occasion it may be excruciating in character. If the pain is not related to dysphagia or the ingestion of food, it may be readily confused with the pain of angina pectoris. This is especially true if the pain has a tendency to extend into the shoulder and arm.

Theoretically, it should be possible to distinguish between the pain of angina pectoris and that of esophageal hiatal hernia by the distribution of the pain down the arm. In hiatal hernia, the pain is referred down the course of the third to the fifth cervical roots from which the phrenic nerve arises and which supply the outer aspect of the shoulder and arm. In angina pectoris, the pain is more likely to be referred down the inner aspect of the arm; in practice the pain is usually so intense or diffuse that the patient experiences great difficulty in delineating its exact borders. Although the pain of angina pectoris is precipitated generally by exertion and that of esophageal hiatal hernia by ingestion of food, this is not invariably true. The problem of differential diagnosis may be complicated by the fact that both the pain of angina pectoris and the pain of hiatal hernia may be relieved by the use of nitroglycerine. Electrocardiographic changes are not a routine accompaniment of hiatal hernia. It must be remembered, however, that hiatal hernia is a disorder that occurs especially in people past middle age, at a period of life when organic heart disease is more prevalent than in younger people. The two conditions may exist in the same individual, and great difficulty may be experienced in deciding which of the two disorders is the cause of the patient's pain. On occasion, interruption of the phrenic nerve is the only method by means of which the pain of angina pectoris and that of hiatal hernia can be distinguished one from the other.

The symptoms produced by hiatal hernia are in a large measure dependent upon the size of the hernia. The larger the hernia, the more likely it is to cause symptoms, even though small hernias are notorious for disregarding the rule. The symptoms of hiatal hernia are influenced also by the type of hernia. The sliding type and acquired short esophagus with intrathoracic stomach (fig. 2) are more prone to cause pain than are congenital short esophagus with intrathoracic stomach and the paraesophageal variety of hiatal hernia (fig. 3).

The diagnosis of esophageal hiatal hernia can be made with a relatively high degree of accuracy by roentgenographic examination. When there is doubt as to the diagnosis or in the determination of the type of hiatal hernia, esophagoscopic examination is always indicated. Such an examination is of value not only in establishing the presence of a hernia but also in determining its type. It is the only method by which it is possible to determine with accuracy the presence of esophagitis or esophageal

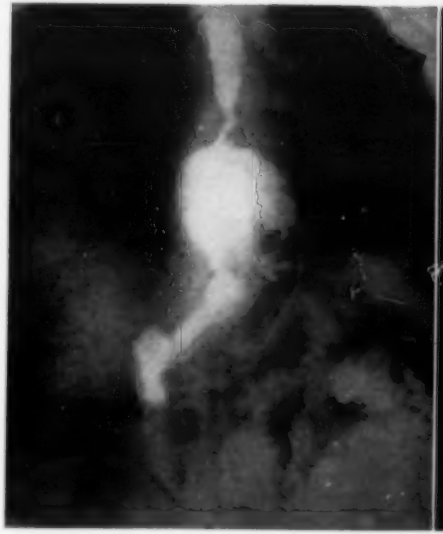

FIGURE 2

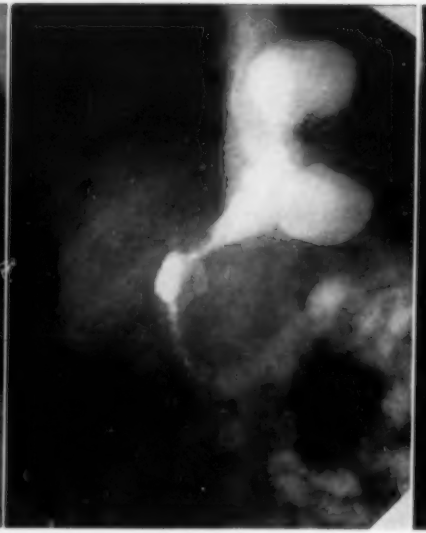

FIGURE 3

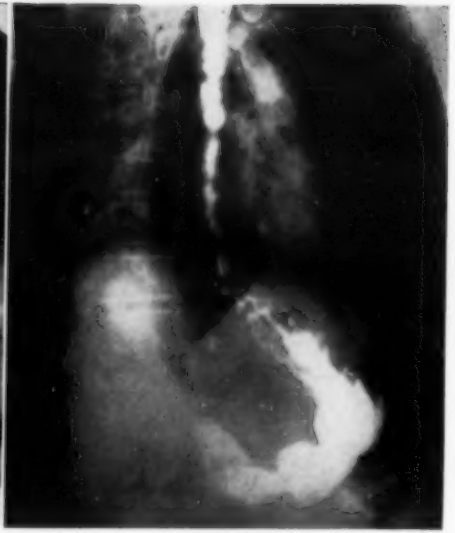

FIGURE 4

Figure 2: Sliding type of hiatal hernia.—*Figure 3:* Paraesophageal type of hiatal hernia.—*Figure 4:* Diffuse spasm of esophagus.

ulceration. It is also of value in determining the presence of an associated carcinoma, foreign body or benign tumor.

Achalasia of the Esophagus

Achalasia of the esophagus, or so-called cardiospasm, may be a cause of anterior thoracic pain. Pain is much more likely to occur in the early stages of a developing achalasia than after the achalasia has become fully developed and dilatation of the esophagus has occurred. Although pain may occur spontaneously in achalasia, it is much more likely to be precipitated by the drinking of cold liquids.

The diagnosis of fully developed achalasia with diffuse dilatation of the esophagus can be made with a high degree of accuracy on roentgenographic examination. Unfortunately, in the early stages of the development of the achalasia, before dilatation of the esophagus has taken place, the roentgen diagnosis is extremely difficult, and it is at this period that pain is most likely to occur. Esophagoscopic examination is of little help in the early diagnosis of achalasia. There are two tests that can be of great help in the identification of early achalasia. The first of these is a study of the motility pattern of the esophagus. In the normal esophagus, with deglutition there is an increase in intraluminal pressure which progresses down the esophagus with the peristaltic wave. In achalasia of the esophagus the intraluminal pressure is not increased with deglutition. The second test that has been found of value in the diagnosis of achalasia is based on the intramuscular injection of methacholine (mecholyl). Kramer and Ingelfinger[1] found that if a patient with achalasia of the esophagus is given an intramuscular injection of 10 mg. of methacholine it will cause the esophagus to be thrown into tetanic contraction. At the same time the patient experiences a very severe retrosternal pain, which closely simulates that seen in angina pectoris. The pain may be so severe as to require the administration of nitroglycerine for relief. These reactions are seldom seen in any type of esophageal disorder other than achalasia.

Diffuse Spasm of the Lower Part of the Esophagus

Diffuse spasm of the lower part of the esophagus is often associated with severe anterior thoracic pain. It is a disorder that is frequently confused with achalasia although in no way related to it. It occurs primarily in patients with very active nervous systems. On roentgenologic examination, the lower third of the esophagus will be found in a state of diffuse spasm (fig. 4). On occasion the spasm may involve the entire gullet. The degree of spasm may vary from time to time. It has been described by some roentgenologists under the term "curling." It is never accompanied by evidence of dilatation of the esophagus as is true in achalasia, and in our experience does not progress into such a condition.

Pain is a very prominent feature of diffuse spasm of the esophagus. The pain may occur both with and without the ingestion of liquids or foods. When dysphagia is present the patient complains that food obstructs at a higher level in the esophagus than in achalasia. The degree

of obstruction varies considerably from time to time, from a slight hesitation in the passage of food through the esophagus to complete esophageal obstruction. Pain may be experienced in the retrosternal region if the food is allowed to remain in the gullet or is forced through into the stomach by the drinking of liquids or by forced deglutition. Often, the pain occurs spontaneously and is not related to eating or drinking. A common experience is for a patient to note some hesitation to the passage of food, which can be overcome by drinking water and be unaccompanied by pain. During the night the patient may be awakened suddenly from a sound sleep by a severe substernal pain which may extend into the neck and into one or both shoulders. The occurrence of such an attack for the first time, especially if the history of dysphagia has been overlooked, is invariably diagnosed as being due to coronary heart disease. Added credence to such a diagnosis would seem to be indicated by the fact that the administration of nitroglycerine relieves the pain.

Esophagoscopic examination is of little value in the diagnosis of diffuse spasm of the esophagus. This is especially true if the examination is performed with the patient under general anesthesia, for then the spasm of the esophagus generally disappears and the esophagoscopic examination will give essentially negative results. More information may be obtained by the passage of a Plummer sound over a previously swallowed silk thread, or by the gentle passage of a stomach tube through the esophagus. Invariably, an obstruction will be detected in the lower part of the esophagus, usually located several inches above the cardia. The obstruction can be overcome by gentle pressure, and as the stomach tube or sound is passed along the course of the esophagus it is repeatedly grasped by contractions of the lower part of the esophagus until the cardia is passed.

Motility studies are of great value in the diagnosis of diffuse spasm of the esophagus. Creamer[2] has pointed out that in diffuse spasm there is with deglutition a simultaneous contraction of the entire lower third of the esophagus, in contrast to an orderly progression of the peristaltic waves with a progressive increase and decrease of intraluminal pressure, as seen in the normal esophagus. In diffuse spasm the increase in intraluminal pressure due to spasm not only is greater but also is more prolonged than occurs in the normal esophagus. In contrast to achalasia, methacholine has no effect upon the esophagus in most cases of diffuse spasm.

It should be pointed out that achalasia that has been treated by forceful dilatation with various types of dilating instruments may be characterized by a roentgenographic picture resembling that of diffuse spasm of the esophagus. Such cases do not, however, demonstrate the typical motility changes found in diffuse spasm.

Esophagitis

A common esophageal disease which may give rise to anterior thoracic pain is esophagitis. The surprising thing is that it is not a more common

cause of such pain. Esophagitis is the most common disorder to afflict the esophagus. Butt and Vinson[3] found it to be present in 7 per cent of their postmortem material. It is a condition that waxes and wanes rapidly. In the great majority of cases it may remain entirely asymptomatic. Again, especially if the esophagitis is severe and associated with ulceration, it may cause severe anterior thoracic pain. The pain is usually described by the patient as being situated deep under the sternum, and often seems to be aggravated by the patient's assuming a recumbent position. It is generally aggravated by the drinking of extremely hot or cold liquids and by the eating of coarse foods. In cases of severe esophagitis the patient may vomit blood or have complete esophageal obstruction due to spasm or secondary cicatrization.

Esophagitis may be caused by a great variety of conditions. It may be produced by the regurgitation of gastric secretions into the esophagus, or it may be the result of ingestion of chemical irritants into the esophagus. It may occur as a manifestation of a generalized infectious process, allergic phenomenon, or part of an obstructive process.

The diagnosis of esophagitis must in most cases depend upon the esophagoscopic findings. Roentgenologic examination of the esophagus is of little value unless ulceration or stricture formation has occurred.

Carcinoma of the Esophagus

Carcinoma of the esophagus may cause anterior thoracic pain. In most cases such pain is a late manifestation of the disease and is associated with dysphagia so that the diagnosis is a relatively simple matter. That pain may be the first symptom of carcinoma of the esophagus and unassociated with dysphagia is less generally appreciated. When pain occurs as the initial symptom of carcinoma of the esophagus, the carcinoma is more likely to be of a type that infiltrates through the wall of the esophagus than of the polypoid type, which projects into the esophageal lumen and causes obstruction.

The pain in carcinoma of the esophagus may be of a boring type which usually extends through to the back. It is usually aggravated by deglutition and often is affected by position. In cases in which the lesion is situated about the cardia, the pain may be referred into the neck or shoulder.

In the early stages of the disease the diagnosis may be difficult, for the absence of dysphagia may seem to exonerate the esophagus. The results of roentgen examination of the esophagus at this period may well prove to be negative. Esophagoscopic examination with removal of secretions and tissue for cytologic and microscopic examination is usually required to establish the diagnosis.

Benign Tumors of the Esophagus

Benign tumors of the esophagus are comparatively rare and seldom produce pain. On occasion, if the tumor is located at the esophageal introitus or at the level of the hiatus in the diaphragm, the patient may

experience discomfort as food passes a constricted site. Very rarely indeed, a patient with a large pedunculated benign tumor may have severe pain if the tumor is regurgitated into the back of the mouth and the patient has difficulty reswallowing it. If the benign tumor undergoes malignant change it may cause pain.

Foreign Bodies of the Esophagus

The possibility of a foreign body must always be considered in any patient who presents a history of sudden dysphagia with associated substernal pain. In most instances in which the patient has swallowed a foreign body that has become lodged in the esophagus, it is possible to obtain a clear-cut story of the accident. On occasion, owing most often to excessive libation or during an accident, the ingestion of the foreign body may be overlooked or forgotten. Generally, when a patient has substernal pain due to the ingestion of a foreign body, the pain is aggravated by deglutition. It often tends to subside in intensity unless perforation of the esophagus is imminent. If the foreign body is opaque it may be detected on roentgen examination of the thorax. Nonopaque foreign bodies can be detected only by esophagoscopic examination or by roentgenoscopic examination of the esophagus with the aid of a swallow of barium.

Miscellaneous Causes

A number of other esophageal disorders may cause anterior thoracic pain. Among these may be mentioned diverticulum of the esophagus, fungous infections and collagen disturbances. Recently we have had two patients who had suppuration of the mediastinal nodes with rupture into the esophagus that was associated with thoracic pain. In both cases the pain subsided with evacuation of the necrotic material into the esophagus. In one of the two cases tubercle bacilli were cultured from the evacuated material.

SUMMARY AND CONCLUSIONS

Esophageal disorders and disease may give rise to pain that is referred to the anterior part of the thorax. The pain may be situated some distance from the site of the esophageal involvement, and may vary considerably in intensity and character. Although pain due to esophageal disease is usually associated with dysphagia, this is not always true. The possibility of an esophageal origin must always be considered in any patient with unexplained anterior thoracic pain.

RESUMEN Y CONCLUSIONES

Los trastornos y afecciones del esófago pueden dar lugar a dolor que puede proyectarse a la pared anterior del tórax. El dolor puede localizarse a cierta distancia del lugar afectado del esófago y puede variar considerablemente en intensidad y caracteres. Aunque el dolor asociado a afección del esófago generalmente se acompaña de disfagia, esto no siempre es cierto. La posibilidad del origen esofágico en un enfermo con dolor torácico anterior no explicado de otra manera, debe conservarse en la mente.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNGEN

Unpässlichkeit und Krankheit der Speiseröhre können Anlass zu Schmerzen geben, die auf dem anterioren Thoraxabschnitt bezogen werden. Der Schmerz kann sich in einigem Abstand von der Stelle der Speiseröhrenaffektion befinden und kann beträchtlich an Intensität und Charakter wechseln. Wenngleich ein durch eine Speiseröhrenerkrankung entstandener Schmerz gewöhnlich mit Schluckbeschwerden verknüpft ist, trifft dies nicht immer zu. Die Möglichkeit eines oesophagealen Ursprungs muss immer in Erwägung gezogen werden bei einem Patienten mit nicht geklärtem Schmerz an der vorderen Brustwand.

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The Future of Cancer Research

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I appreciate the honor you have paid me by your invitation to participate in this program. I have seen familiar faces here and am happy to have the opportunity of seeing old friends again and meeting new ones.

Discussion of the future of cancer research must of necessity be speculative. But, I am reminded of a comment by Winston Churchill in an address to the Royal College of Physicians some years ago, in which he said, "The longer you can look back, the further you can look forward." With this thought in mind, that the past furnishes the key to the present and the future, I shall review some aspects of cancer research.

These will include (1) a brief description of some of the important areas of cancer research that may produce the advances of the future, (2) a summary of some highlights of progress in these areas, and (3) a discussion of the lung cancer problem—a particularly pertinent subject, in view of the alarming rise of this type of cancer in recent years and the special interest of this audience in diseases of the chest.

Chemotherapy

Chemotherapy is one of the most active and promising areas in cancer research today. In this area, the National Cancer Institute has taken an active part in developing a national program of voluntary cooperative research. With its cosponsors—the American Cancer Society, Damon Runyon Memorial Fund for Cancer Research, Veterans Administration, Atomic Energy Commission, and Food and Drug Administration—the Institute has organized the Cancer Chemotherapy National Service Center, located in Bethesda on the grounds of the National Institutes of Health and staffed jointly by the sponsoring agencies.

The program is based on the concept that, through encouraging voluntary cooperative group studies in certain areas and at the same time giving support to individual investigators, research in cancer chemotherapy may be accelerated. Essentially, there are two aspects to the program: the support of basic research throughout the country by grants of funds and the screening, pharmacological work-up, and clinical evaluation of drugs.

Some 25,000 chemicals and antibiotic filtrates are furnished annually to the Service Center by the pharmaceutical industry and university laboratories. Compounds that have been found active when screened against selected types of mouse cancer and subsequently found to be non-toxic in animals are evaluated in volunteer patients. In some studies, the com-

*Director, National Cancer Institute, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare. Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.

pounds are compared with one or more agents known to be active; in other studies, they are evaluated in conjunction with surgery and/or radiation. For these clinical trials nine cooperative study groups and two cooperative groups in the Veterans Administration have been formed, representing more than 75 medical schools and hospitals located in different parts of the country. Analysis of data on end-results is being accomplished through tumor registries set up to provide data annually on all types of cancer, and to undertake special studies on the effects of various treatments.

Research activity in the United States and England, in particular, has produced about two dozen chemotherapeutic agents in the last few years. These compounds are useful temporarily in alleviating symptoms and in many cases prolonging the useful life of patients suffering from about 15 types of cancer, including leukemia, Hodgkin's disease, and advanced cancers of the breast and prostate gland. The compounds include adrenal steroids and ACTH, antimetabolites, alkylating agents, radioactive isotopes, hormonal alterants, and cell poisons. The majority of these were developed within the last decade; some of them are nitrogen mustards, methotrexate, aminopterin, 6-mercaptopurine, myleran, CB-1348, and azaserine.

An exciting advance that may be a real breakthrough in chemotherapy was reported recently by National Cancer Institute scientists. These workers presented evidence that for the first time a malignant solid tumor has been apparently suppressed in several patients by drug treatment. This result was obtained in four women with advanced and widespread choriocarcinoma, a rare tumor which occurs in the uterus of women after pregnancy.

An important index for evaluating progress of treatment was provided by the hormone—chorionic gonadotropin—which the cancer produces and the patient excretes in the urine. Quantitative measurement of this hormone and of palpable tumors, as well as x-rays, were used as indices of response of the cancer to treatment.

The drug was a folic acid antagonist, methotrexate, which was developed within the last decade and in many instances successfully used to increase the survival time of children suffering from acute leukemia. In this study, methotrexate was given by injection or mouth under a newly devised schedule, in which a large dose was administered in equal portions over a period of five days and repeated at about two-week intervals for two months or more.

Three women showed suppression of cancer and disappearance of metastases for 12, 13, and 17 months, respectively. The metastases included secondary lesions in the lungs and pelvis. The fourth woman has been treated recently and her cancer has been similarly suppressed.

Cytology

Cytology is another promising area of cancer research. The cytologic test was first suggested by Papanicolaou as a diagnostic tool more than

30 years ago, but its use has become widespread only in the last dozen years. The method involves the microscopic examination of a smear containing cells exfoliated from certain internal organs and collected from various openings of the body. These cells are obtained by aspiration or scraping.

The most significant and fruitful use of the cytologic technique has been as an aid in the diagnosis of uterine cervical cancer in its earliest and most curable stages. Uterine cancer is the second leading cause of death from cancer in women.

Since 1952, a large-scale study of vaginal smears obtained by aspiration has been carried out in the Memphis area by the National Cancer Institute with the cooperation of the University of Tennessee and other local medical and health groups.

Figure 1 shows the most recent results in the Memphis study, summarizing the findings obtained in the first examination of 108,000 women. About 800 cases of cancer were discovered; these were equally divided between intraepithelial carcinomas and invasive uterine cancers. Of the early stage cancers, fully 90 per cent were totally unsuspected by physician or patient; of the advanced cancers, about 30 per cent were unsuspected.

The second screening of 33,000 women has led to the diagnosis of 83 cases of cancer, of which 72 were early stage cervical cancer and 11 were advanced uterine cancer. Analysis of the data from the third testing of 8,000 women is not yet complete.

Two observations concerning the efficiency of this technique as a case-finding procedure are noteworthy. One is that the Memphis study produced a case-finding rate for early cervical cancer 40 times that observed

MEMPHIS UTERINE CANCER SCREENING PROJECT

Pathological Findings in 1,453 of 1,842 Women for Whom Biopsies Were Recommended as a Result of Examination of Vaginal Smears of 108,136 Women

	Number		Per Cent of 108,000 Women
Invasive uterine cancer	373		0.34
Cancer of cervix		331	0.31
Cancer of corpus		42	0.04
Other genital cancers	20		0.02
Intraepithelial carcinoma of cervix	393		0.36
Total cancer and intraepithelial carcinoma	786		0.73
Atypical metaplasia	141		0.13
Findings normal	479		0.44
TOTAL	1,406*		1.30

*Biopsies were inadequate in 47 women.

FIGURE 1

in the community before establishment of the project. The other is that the case-finding rate in the second screening was significantly lower than in the first screening. Comparing the first and second screenings, the investigators found the rates for early stage cancer to be 3.6 and 2.2, respectively, per 1,000 women; and for advanced cancer, 3.1 and 0.3, respectively, per 1,000 women. The data indicate clearly that the cytologic test is valuable as a means of detecting early cervical cancer.

In addition to uncovering many unsuspected cancers, the study corroborated the observation that intraepithelial carcinoma, or carcinoma-in-situ, lasts several years—long enough to permit effective curative treatment in virtually 100 per cent of cases if discovered at the yearly checkup.

The vaginal cytology studies are being expanded by the National Cancer Institute in several other projects to provide additional data on the incidence and natural history of uterine cervical cancer. In addition, variations of the cytologic method to aid in the diagnosis of cancer involving other sites in the body are under study. These sites include the lung, large intestine, prostate, and bladder. The usefulness of the technique for these sites is limited to symptomatic individuals because of the difficulty of obtaining and processing specimens for examination. However, encouraging results are being obtained, for example, in the cytologic examination of repeated sputum specimens in bronchogenic carcinoma.

Figure 2 shows an electronic scanner which is being developed under grants from the National Cancer Institute and the American Cancer Society to facilitate the screening of the microscopic slides. This instrument, called the cytoanalyzer, will rapidly scan the microscope image of cells, automatically sort them according to their characteristics, and then classify them as normal or suspicious. The development of the instrument has not yet been completed, but prototypes will be used in the Memphis study and at the Strang Clinic of the Memorial Center late this summer.

Virology

Virology is still another extremely important area in cancer research. Its influence is felt not only in research on the causes and therapy of cancer, but also in basic studies of the very nature of life itself. The common denominator link appears to be the huge molecules known as nucleoproteins which are basic constituents of living matter and are also the essential component of viruses.

Whether viruses cause cancer in man still remains to be demonstrated. A persuasive argument for the acceptance of the viral etiology of cancer was presented recently by Nobelist Wendell Stanley in a review of a half-century of research that began with the discovery of the Rous sarcoma virus in fowls. He concluded his lecture with following provocative com ments: "The recent findings in the virus field indicate more and more that the virus problem and the cancer problem are one and the same. The experimental evidence now available is consistent with the idea that viruses are the etiologic agents of most, if not all, cancer, including cancer in man."

Recent research on the viral therapy of cancer has accomplished the "training" of a virus to destroy a human tumor growing in rats. In a project carried out jointly by scientists of the National Cancer Institute and the National Institute of Allergy and Infectious Diseases, the tumors were produced by intraperitoneal inoculation of suspensions of HeLa cells into cortisone-treated, irradiated rats. HeLa cells are cancer cells that have been kept alive in tissue culture since 1951, when they were removed from a patient who had carcinoma of the cervix. Coxsackie B3 virus was passed serially several times through the tumors growing in the rats, whereupon the virus developed the capacity to produce gross and histological evidence of oncolysis. The experimental evidence was pretty clear that the virus actually produced infection and destroyed the cancer cells, instead of acting by stimulating the defenses of the host animal.

Immunology

Immunology is a relative newcomer among the important areas in cancer research. Precise studies of the blood and blood serum, made possible by the development of new techniques, have aroused much interest in cancer immunology. Why do some persons have greater immunity to

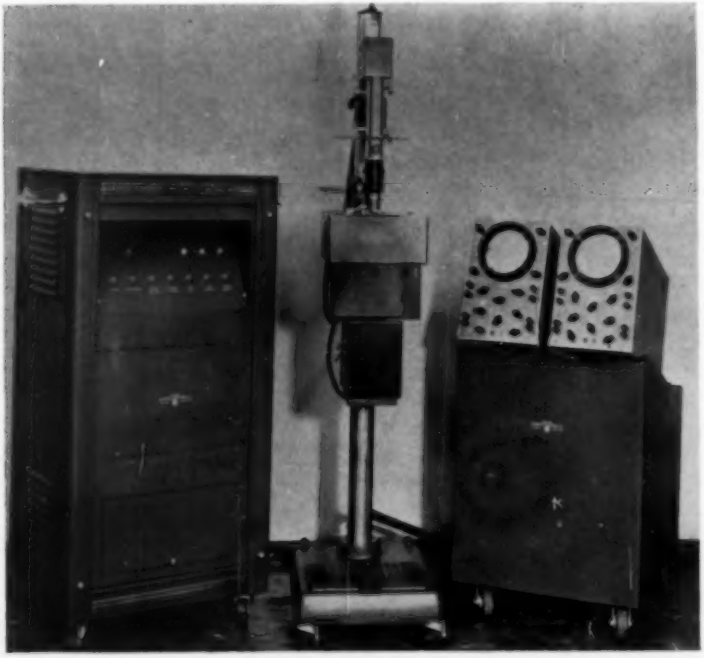

FIGURE 2
Cytoanalyzer

cancer than others? Does resistance or susceptibility to infection and to cancer involve similar factors in the host? Will it be possible to develop a vaccine effective against human cancer? These are a few of the questions that may produce important developments of the future.

Recently, National Cancer Institute scientists reported a finding that may influence the course of future studies of cancer immunity. In a comprehensive, systematic investigation, they were studying the properties of polysaccharides from various sources. Polysaccharides are complex sugars of high molecular size. They were isolated many years ago from gram-negative bacteria and they not only produce reactions characteristic of infectious bacteria but also damage cancer tissue.

These investigators have now found that regardless of the source of the polysaccharides—bacteria, plant tissues, or normal or cancerous animal tissues—they all produced in laboratory animals the reactions hitherto considered characteristic of bacterial polysaccharides. Twelve reactions were studied, including fever, changes in blood properdin levels, changes in resistance to infection, and tumor damage. These findings suggest that some factors involved in infection and in tumor damage appear to be related and that these polysaccharides constitute an underlying feature common to many situations injurious to man, such as infection, cancer, and various kinds of shock.

Development of a vaccine which has proved 80 per cent effective in protecting mice against leukemia was reported by an investigator whose research is supported in part by a grant from the National Cancer Institute. About a year ago this scientist discovered a disease of mice which had the characteristics of a leukemia and was transmissible to adult mice by means of a cell-free agent. A small number of mice inoculated with the agent were found to have remained free of the disease. When it was found that these animals showed immunity to reinfection upon challenge with active material, a study of the antigenic properties of the agent was undertaken and the vaccine was developed. The vaccine, a formalin-killed virus preparation, was given in a series of three injections at weekly intervals. The mice were then challenged with live virus. About four-fifths of the animals proved to be immune even as long as four weeks after vaccination.

The potential of these areas—chemotherapy, cytology, virology, and immunology—is unlimited. In addition, we may expect substantial achievements from the search for possible cancer-causing agents in the environment in which we live and work, and from improvements in radiological and surgical techniques in the management of cancer. With the knowledge that has been accumulated until now in these various areas, how far have we progressed in saving lives from cancer?

Epidemiology

Results of a study in another important area of cancer research, epidemiology, throw some light on this subject. In cooperation with the Connecticut State Cancer Register, the National Cancer Institute ana-

lyzed the medical records of some 75,000 cancer patients, 95 per cent of whom were successfully followed for five years or more. The Register data cover a span of approximately 20 years. The results are interpreted as an indication of better treatment of an increasingly greater proportion of cancer patients.

Figure 3 shows that the five-year survival rate for cancer patients is improving significantly. In the 20-year period, the survival rates for all cancers combined rose from 19 to 25 per cent for males and from 29 to 38 per cent for females. The average for all cancer patients was 32 per cent.

Marked increases in the five-year survival rates were noted for cancer of the large intestine, uterine cervix, and rectum; noteworthy improvement for cancer of the uterus and prostate. No improvement was noted for cancer of the lung, stomach, bone, and brain.

Lung Cancer

It is of particular interest to this audience, to note that the improvement in management of lung cancer has been meager. It is equally important to this audience, both personally and professionally, to realize that the greatest threat from cancer among men over 45 years of age is primary carcinoma of the lung.

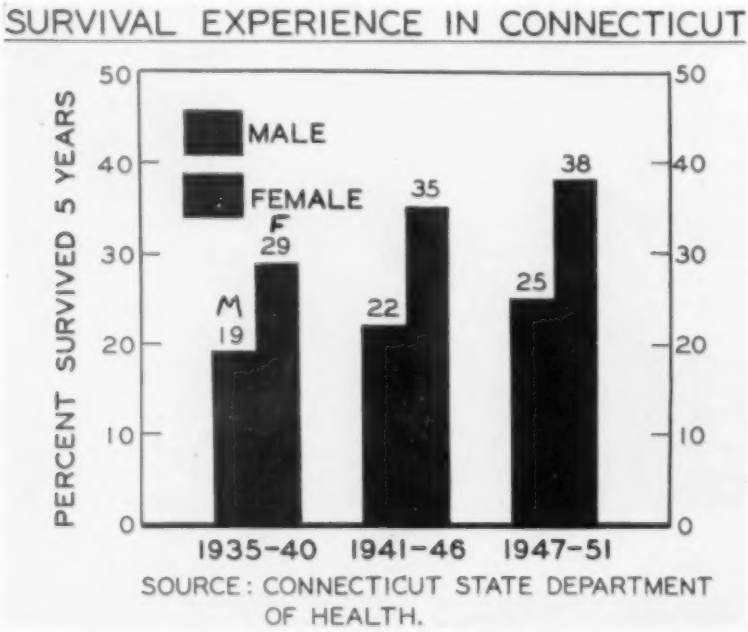

FIGURE 3

Rise in Lung Cancer

Since 1914, when deaths attributed to cancer of the respiratory system were identified separately for the first time, deaths from lung cancer have increased sharply.

Figure 4 shows that this trend is in contrast to death rates for white males in the period 1914 to 1952, for other respiratory diseases, including influenza, pneumonia, and tuberculosis.

During the last two decades alone the rate of lung cancer mortality in the United States increased by more than 400 per cent. In 1930 less than 3,000 deaths were ascribed to lung cancer; in 1955, 27,000 deaths from lung cancer were reported. Although part of the reported increase is undoubtedly due to improved diagnostic techniques and to greater alertness on the part of physicians, leading investigators believe that a significant part of the observed increase represents a real increase in the rate at which lung cancer is developing in the population.

The lung cancer death rate in males is about 4.5 times that in females. Up to age 40, lung cancer is rare in persons of both sexes. Among males, the mortality curve rises very rapidly between ages 40 and 70 and then declines almost as rapidly. In contrast, the curve for females resembles that for all forms of cancer combined, showing a slower but steady rise over the entire life span.

Figure 5 shows the increase in incidence of cancer of the respiratory

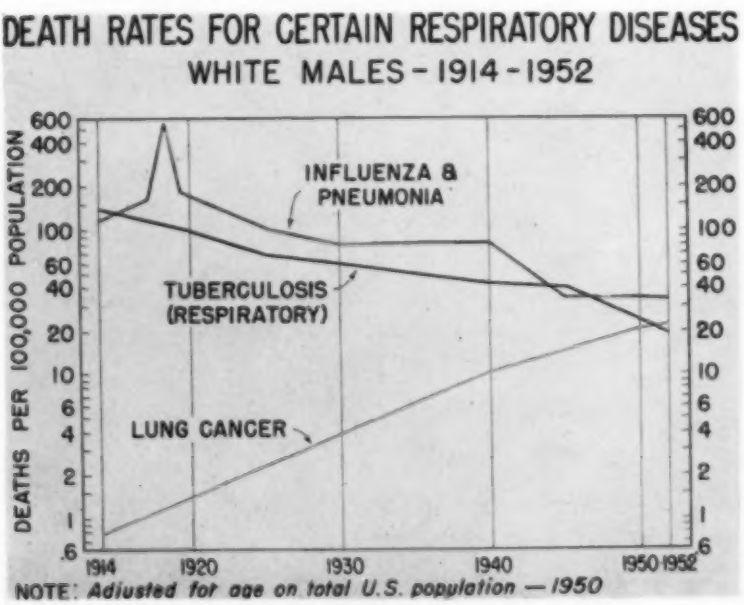

FIGURE 4

system in the 10-year period, 1937-1947. The results were obtained in a series of cancer morbidity surveys in 10 metropolitan areas representing different geographical regions of the United States. The increase was 66 per cent for all persons, 73 per cent for males, and 51 per cent for females.

Figure 6 shows the increase in incidence of cancer of the lung observed in the same surveys. The increase was 105 per cent for all persons, 119 per cent for males, and 67 per cent for females.

Figure 7 shows a comparison of the incidence rates of lung cancer in white males observed in the same surveys and the estimated rates for the cohort (persons born in the same year or group of years) of 1910. The rate of incidence increases sharply at around age 45. From age 55, the rate for cohort 1910 increases sharply, and at age 75, the projected rate for cohort 1910 is more than twice the rate observed in 1947.

From these data it was estimated that 11 of every 1,000 white males born in 1910 may be expected to develop lung cancer by age 60, 27 by age 70 and 43 by age 80.

Investigators in cancer research are attacking the problem in several ways. These include studies of environmental factors, on the assumption that prevention may be possible by elimination of cancer-causing hazards from the environment; and studies of improved diagnostic and therapeutic procedures, which are designed not only to shorten the interval between onset and treatment of the disease but also to make treatment more effective.

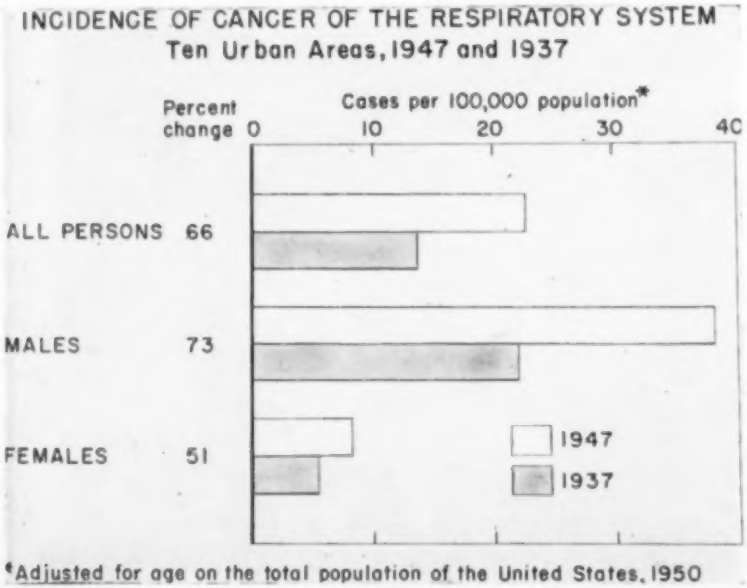

FIGURE 5

Causes

The possible environmental changes, not mutually exclusive, which have been suggested as causal factors in the sharp rise in lung cancer, fall into three major categories: (1) increased use of cigarettes; (2) increased atmospheric pollution by the effluents of an industrial civilization, such as motor vehicle exhausts and factory wastes; (3) increase in special occupational hazards involving industrial exposure in producing or processing chromate ores, radioactive ores, and certain dyes.

Of the evidence available, that which links cigarette smoking to lung cancer appears to be most convincing. At least 16 independent studies carried on in five countries during the past 18 years have shown that there is a statistical association between smoking and the occurrence of lung cancer.

Lung cancer occurs much more frequently—five to 15 times—among cigarette smokers than among nonsmokers, and there is direct relationship between the incidence of lung cancer and the amount smoked. It has been estimated recently that on a lifetime basis, one of every 10 men who smoke over two packs a day will die of lung cancer. The comparable risk among nonsmokers is estimated at one in 275.

Diagnosis

Improved diagnostic procedures are being investigated assiduously, since early bronchogenic carcinoma is two to five times as curable as are symp-

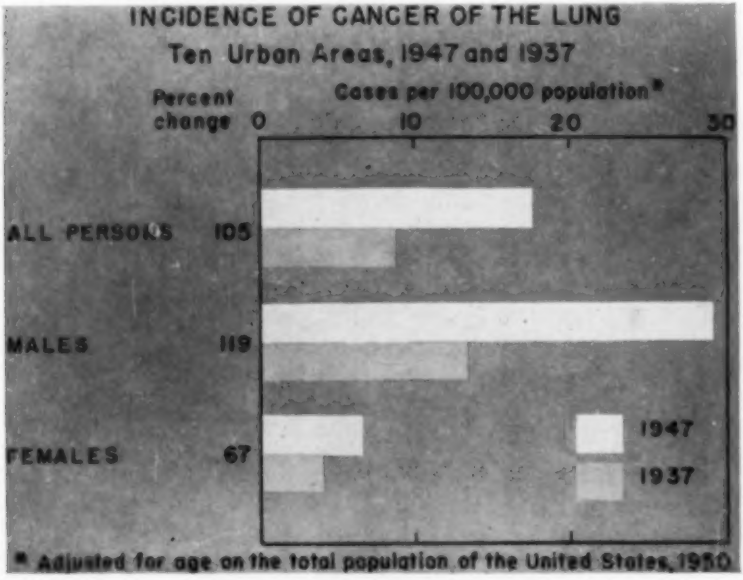

FIGURE 6

tomatic, long-suspected cancers. In symptomatic patients, it is now definitely established that cytology is a valuable aid in the diagnosis of cancer of the lung. Although cytopathologists may disagree as to whether sputum or bronchial aspirates provide the best source of specimens for examination, it seems that they each have certain advantages and may give comparably good results. In the application of cytology for screening asymptomatic people, research is under way in numerous laboratories to solve the problems involved in recognizing preneoplastic changes and intraepithelial carcinoma, and developing methods of obtaining suitable specimens and screening them.

The development of a supervoltage radiation machine powerful enough to reveal deep-seated lung cancers in their early stages was recently described. This x-ray machine is characterized by excellent mediastinal penetration and a minimum of glare. Results of a recent clinical study with it were reported to be encouraging enough to justify further study.

Therapy

Supervoltage radiation is also being applied as a therapeutic weapon. In a research project reported by a grantee of the National Cancer Institute, a group of 100 patients with advanced inoperable lung cancer were irradiated with dosages to the tumor of 4,000 to 6,000 roentgens from a

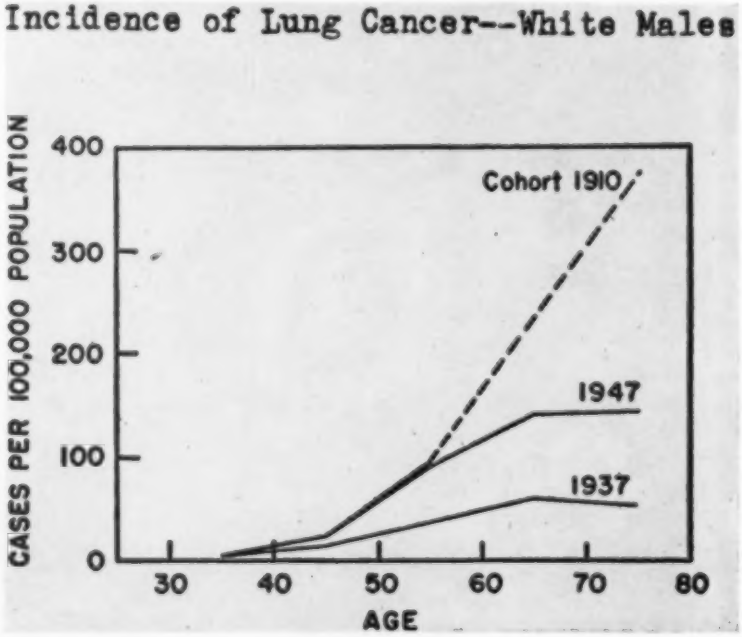

FIGURE 7

2,000-kilovolt machine. Eighty-four of these patients were followed for more than three months, and 63 of them showed definite benefit from the radiation therapy. Twenty-seven patients lived longer than one year, and of these 17 survived two years or more. All the patients who lived longer than 18 months received a tumor dosage of at least 5,000 roentgens in five weeks' time. Age, sex, and location of tumor did not seem to have had any effect upon success or failure of therapy. At the time of reporting, 24 patients were alive, the elapsed time since completion of their treatment averaging more than 12 months, and 19 patients were completely free of symptoms.

Nature of Cancer Research

Before concluding, I should like to share a few additional thoughts with you on the nature of cancer research.

Those of us who spend our lives wrestling with the cancer problem believe that cancer is vulnerable and that it is already yielding here and there against the weight of our forces. In order that you may understand our optimism, you should realize first of all that the climate for cancer research is more favorable now than at any time in the history of medical research. The reasons are mainly three-fold: we have funds; we are training research scientists; and we are developing techniques and tools.

First, ample financial support is available from both public and private sources for carrying on comprehensive laboratory and clinical research programs. Currently, about $46 million is being spent for cancer research. Of this amount, $35 million is contributed by the United States Government, represented chiefly by the National Cancer Institute, Atomic Energy Commission, and Veterans Administration. Another $11 million is contributed by leading voluntary agencies and private foundations, including, for example, the American Cancer Society, Damon Runyon Memorial Fund, Tobacco Industry Research Committee, and Sloan-Kettering Institute.

Second, training programs are being expanded to increase the supply of cancer research manpower. The National Cancer Institute supports four types of such programs. These include undergraduate training grants to medical, dental, and osteopathic schools for assistance in expanding and integrating instruction in cancer; clinical traineeships to young physicians for special training in detection, diagnosis, and treatment of neoplastic diseases; research fellowships to scientists for special research training; and research training grants to research institutions, which select and appoint individual scientists for training. The program for awarding research training grants was established in 1956 and has so far disbursed 15 grants which totaled just under $1 million. The program extends and supplements but does not replace the research training opportunities available through the research fellowships.

Third, new and refined research techniques and instruments have been developed rapidly since World War II. These include supervoltage generators, radioisotopes, the electron microscope, and other electronic de-

vices, inbred strains of mice, tissue culture, chromatography, mass spectograph, and, most recently, an ultraviolet television camera-microscope, to name just a few. In addition, development of the new concept of molecular biology has brought the precise techniques of biochemistry to the characterization of cell processes in terms of molecules and their chemical interactions.

Another important aspect of cancer research is its cooperative nature. If one were to follow the one outstanding "tagged element" which threads its way throughout the length and breadth of the fabric of cancer research, he would find it to be "cooperative effort."

Cancer research is financed by cooperative funds, coordinated by cooperating organizations, and performed by cooperating skills. In fact, it is not a science in itself, but the simultaneous activity of many independent scientific disciplines. Cancer research began as an experimental science at the close of the 19th century with the study of animal tumors. Step by step new specialties have been added until now they cover a wide range of biological, medical, and physical sciences.

The variety of achievements cited in this brief review illustrates eloquently the nature of cancer research. These include the suppression of a solid malignant tumor by drug treatment; application of cytology to detect early cancer of the uterine cervix; "training of a virus to destroy human cancer growing in rats; observation of a possible relationship between the factors involved in infection and cancer; development of a vaccine that protects mice against leukemia; and establishment of a statistical association between cigarette smoking and lung cancer.

Our outlook for the future is optimistic. All the factors involved in organizing and carrying on cancer research have combined synergistically to produce a great, sustained effort which is only beginning to reach its full stride. "It is a bold prophet who would set limits to the future advance of medical science."

SUMMARY

Some important areas of cancer research that may produce the advances of the future are chemotherapy, cytology, virology, and immunology. Recent progress in these areas is illustrated by a variety of achievements.

One of these is the suppression of choriocarcinoma, a rare, solid malignant tumor of embryonic origin, by treatment with methotrexate. Another is the application of exfoliative cytology to detect early cancer of the uterine cervix. In another recent accomplishment, the Coxsackie B3 virus was passed serially several times through human tumors growing in rats and so "trained" to destroy these tumors in the rats.

Another finding is the observation of a possible relationship between the factors involved in infection and cancer. Studies of the properties of the complex, high molecular weight sugars, known as polysaccharides, showed that they produced in laboratory animals not only reactions characteristic of infectious bacteria but also tumor damage.

Cancer of the lung is being studied intensively in a variety of ways, in efforts to combat the sharp rise in this type of cancer that has occurred particularly among men over 45 years of age. Epidemiological studies have established a statistical association between cigarette smoking and lung cancer. Also, studies are under way to improve diagnostic and therapeutic procedures, designed to shorten the interval between onset and treatment of the disease, and to make treatment more effective.

The many kinds of achievements amply illustrate the cooperative nature of cancer research. In fact, it is not a science in itself, but the simultaneous activity of many independent scientific disciplines.

RESUMEN

Ciertos campos de investigación en cáncer que pueden conducir a adelantos son la quimioterapia, la citología y la inmunobiología. Se ilustran los recientes progresos en estos campos por una variedad de adquisiciones.

Una de ellas es la supresión del coriocarcinoma, un tumor raro, sólido y maligno de origen embrionario, mediante el tratamiento con metotrexato. Otra es la aplicación de la citología de exfoliación para descubrir tempranamente el cáncer cervical. En otra experiencia el virus B3 Coxsackie se hizo pasar varias veces por tumores humans injertados en ratas y así "amaestrados" para destruir esos tumores en las ratas.

Otro hallazgo es la observación de posible relación entre los factores actuantes de la infección y en el cáncer. Los estudios de las propiedades de los azúcares de elevado peso molecular conocidos como polisacárridos, demonstraron que ellos producen en los animales de laboratorio no sólo reacciones características de las bacterias infecciosas sino también daño tumoral.

El cáncer del pumón se estudia de diversas maneras esforzándose por combatir el aumento notable de este tipo de cáncer, aumento que ha ocurrido especialmente entre los hombres de más de 45 años. Los estudios epidemiológicos han demonstrado una asociación estadística entre el fumar cigarrillos y el cáncer. Hay también estudios en marcha para mejorar los procedimientos de diagnóstico y tratamiento y para hacer el tratamiento más efectivo.

Las muchas clases de adquisiciones muestran con amplitud la naturaleza cooperativa de la investigación del cáncer.

De hecho, no es una ciencia por sí, sino la simultánea actividad de muchas disciplinas científicas independientes.

RESUME

Les éléments importants qui peuvent amener des progrès futurs dans la recherche sur le cancer, sont la chimiothérapie, la cytologie, la virologie et l'immunologie. De récents progrès dans ces domaines sont illustrés par une série de succès.

L'un d'entre eux est la suppression du choriocarcinome, tumeur maligne

rare, d'origine embryonaire, par le traitement par le méthotrexate. Une autre est l'application de la cytologie exfoliative pour mettre en évidence un cancer précoce du col de l'utérus. Dans une autre étude récente, on fit passer en série le virus Coxsackie B3 plusieurs fois àtravers des tumeurs humaines développées chez les rats, et il fut ainsi "entrainé" à détruire ces tumeurs.

Une autre découverte est l'observation d'un rapport possible entre les facteurs concernant l'infection et le cancer. Des études sur les propriétés des sucres complexes, à poids moléculaire élevé, connus sous le terme de polysaccharides, montrèrent qu'ils produisent chez les animaux de laboratoire non seulement des réactions caractéristiques des infections bactériennes, mais aussi des manifestations tumorales.

On est en train d'étudier intensivement le cancer du poumon, dans des voies diverses, pour combattre l'augmentation en flèche de ce type de cancer qui survient particulièrement chez les hommes âgés de plus de 45 ans. Des études épidémiologiques ont établi une association statistique entre la fumée de cigarette et le cancer pulmonaire. Egalement des études sont en cours pour améliorer les moyens de diagnostic et de thérapeutique, destinés à raccourcir l'intervalle entre l'apparition de l'affection et le traitement, et pour augmenter l'efficacité du traitement.

Le grand nombre des succès illustre amplement la valeur de la coopération dans la recherche du cancer. En fait, ce n'est pas une science en elle-même, mais l'activité simultanée de beaucoup de disciplines scientifiques indépendantes.

ZUSAMMENFASSUNG

Einige wichtige Gebiete der Krebsforschung, die die Fortschritte der Zukunft bilden können, sind die Chemotherapie, Cytologie, Virusforschung und Immunologie. Die kürzlichen Fortschritte auf diesen Gebieten werden anschaulich gemacht durch eine Vielzahl von Leistungen.

Eine von diesen ist die Hemmung des Chorion-Carcinomas, eines seltenen, soliden, bösartigen Tumors, embryonalen Ursprungs durch Behandlung mit Methotrexat. Eine andere ist die Anwendung der Cytologie abgestossener Ephitelien zur Entdeckung eines früheren Gebärmutterhalskrebses. In der kürzlich erfolgten Erreichung eines anderen Zieles lies man das Coxsacjie-B3-Virus periodisch nemrere Male durch bei Ratten wachsende menschliche Tumoren passieren und "Trainierte" sie so, diese Tumoren bei den Ratten zu zerstören.

Ein anderer Befund ist die Beobachtung einer möglichen Beziehung zwischen den bei der Infektion und dem Krebs beteiligten Faktoren. Studien über die Eigenschaften der complexen Zuckerverbindungen von hohem Molekular-Gewicht, die als Polysaccharide bekannt sind, ergab, dass sie bei Laboratoriumstieren nicht nur Reaktion entwickelten, die charakteristisch waren für infektiöse Bakterien, sondern auch den Tumor schädigten. Intensive Untersuchungen über den Lungenkrebs sind auf einer Vielzahl von Wegen im Gange mit dem Bemühen, den steilen Anstieg dieser Krebsart zu bekämpfen, der sich besonders bei Männern

über 45 Jahren ereignet hat. Epidemilogische Untersuchungen haben ein statistische Beziehung begründet zwischen dem Zigarettenrauchen und dem Lungenkrebs. Ausserdem sind Untersuchungen im Gang zur Verbesserung der diagnostischen und therapeutischen Massnahmen mit dem Ziel, den Zeitabstand zu verkürzen zwischen dem Beginn und der Behandlung der Krankheit, und um die Behandlung wirksamer zu gestalten.

Die Vielzahl von Leistungen veranschaulicht zur Genüge die cooperative Natur der Krebsforschung. Sie ist in der Tat keine Wissenschaft für sich allein, sondern besteht aus der Tätigkeit vieler für sich bestehender wissenschaftlicher Disziplinen.

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Clinical and Biological Investigations on the New Antituberculosis Drugs (Pyrazinamide and Cycloserine)

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Pyrazinamide

Up to now at the Carlo Forlanini Institute, about 100 patients have been treated with pyrazinamide.† Here we will report only a first group of 30 patients having undergone a whole regimen of therapy (four to six months), and for whom a number of biological tests were carried out that will be reported elsewhere.

The above mentioned 30 patients (15 men and 15 women) were affected by various forms of pulmonary tuberculosis, of which 11 were moderately advanced (one essentially exudative, ten essentially productive) and 19 chronic (six essentially exudative, two with residual cavitation, one tuberculoma). Of these chronic forms, four (two productive, two exudative) showed some exacerbation phenomena at the start of pyrazinamide therapy.

All patients had already received prior therapy with other antibiotics and antituberculosis chemotherapeutic agents, and most of them had presented tubercle bacilli in sputum more or less resistant to streptomycin, isoniazid and PAS. Except for some cases without clinical findings, the objective auscultatory findings of the lungs were quite prominent. Patients were carefully selected so as to eliminate any that had evidence of hepatic dysfunction. The daily dose of the drug (divided into five times a day) was 2.5 gr. gradually reached at the fourth day of treatment. In addition to routine roentgenographic, planigraphic and laboratory examinations (B.U.N., F.B.S., urine, and sputum analyses), repeated controls were carried out. These were related to the peripheral blood count, serum electrophoresis, the phagocytosis index, Middlebrook-Dubos test, P.B.I. urinary 17-ketosteroids, behavior of the specific proteases, serum lipase power, serum cholesterol, serum bilirubin, plasma fibrinogen, prothrombin time, colloidal serolability tests, hippuric acid and B.S.P. tests.

In Table I the important clinical roentgenographic and laboratory results are summarized, before and after 80 days of therapy.

The drug tolerance in the doses we used was generally good, except for appearance of arthralgic phenomena in three patients; in one, symptoms started after a few days' treatment and were present in the articulations of the upper and lower members, but without tumefaction. It is to be noted that such arthralgic phenomena completely disappeared with

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†The reported data correspond to the first of December, 1956.

the temporary suspension of therapy. In another patient, therapy was restarted after a 20-day interval. A clinical picture of acute hypoadrenal corticalism was noted, featured by severe asthenia, marked hypotension, dyspepsia, generalized hyper-pigmentation, marked decrease of the urinary 17- ketosteroids, and by an alteration of serum electrolytes, principally saline.

In regard to the incidence of hepatic disturbances as outlined in the literature, we observed one case with abnormal bromsuphalein retention. In two other patients, jaundice with high fever was noted at the 42nd and at the 90th day of therapy, after some early symptoms of asthenia, anorexia, and dyspepsia. In both cases, the pyrazinamide administration was stopped. Furthermore, in two other patients, one could observe the temporary formation of edema and in a third one, an urticaria of short duration. A pertinent observation, limited to the female patients, is the manifestation of brown pigmentation of the skin of the body exposed to the light (face, neck, hands); this phenomenon slowly regressed after the cessation of therapy.

In view of the absence of any evidence of hypo-adrenal corticalism as determined by our tests, and in consideration that the pigmentation was limited to the skin exposed to the sun, this phenomenon has been interpreted by us as an increase of the photo-sensitivity of the skin. It could be possible that a metabolic alteration of vitamin PP was also a factor.

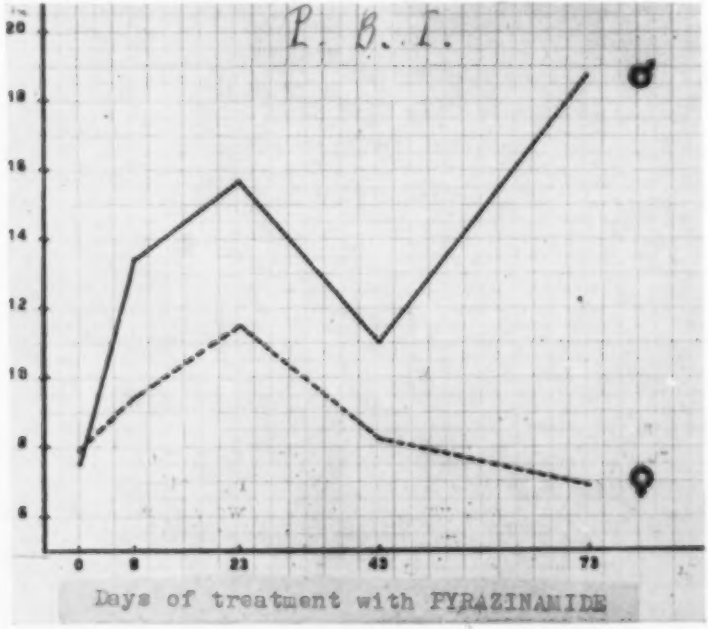

FIGURE 1

TABLE I

Clinical and Laboratory Data	Prior to Pyrazinamide Treatment		Number of Cases	After Pyrazinamide Treatment		Number of Cases
General conditions (cenesthesia, forces appetite, dynamism, toxiemic status)	Good Mediocre Decayed		11 8 11	Improved Unchanged Worse		20 6 4
Local conditions — Clinical Report				Temporarily improved Improved Unchanged Worse		2 10 15 3
Local conditions — RX				Transiently improved Improved Unchanged Worse Cavity regression (included in improved subjects)		3 7 13 7 3
Fever temperature	Present Absent		8 22	Appeared Disappeared Temporarily disappeared Decreased Unchanged		2 3 2 0 23
Coughing and expectoration Tubercle bacilli research in the expectoration	Positive	direct on culture	69,23% 58,83%	Increased Unchanged Decreased Disappeared Haemophtisis of slight entity		5 8 10 7 2
	Negative	direct on culture	30,76% 41,17%	Positive	direct on culture	61,53% 58,83%
				Negative	direct on culture	38,47% 41,17%
Weight				Increased Unchanged Decreased		15 6 9
S. R.				Increased Unchanged Decreased		12 6 12
Toxic phenomena				Artralgia Jaundice Urticaria Asthenia Dispeptic troubles Oedema appearance Hyperpigmentation of uncovered sides to light		3 2 1 2 5 2 12
Glycemia				Meaning-less oscillations		
Azotemia				Did not show particular variations as for starting values		
Urinary findings				Albuminaria increase in 30% of cases; appearance of urobilinuria in 5 cases, of biliary pigments in 3 cases and of haematuria in 4 cases		

In the course of the clinical experiment, a number of biologic investigations were carried out, the results of which are presented in the following summary:

1) *The precipitable bound iodine* elevated until the 23rd day of therapy (higher in males than in females) and after a short decrease from the 43rd day, it demonstrated a dissociated behavior in the two sexes, in the sense of a marked increase for the males and of a further reduction for the females (Figure 1).

2) *The serum cholesterol and cholesterol-esters,* after a slight fluctuation within the the first week, serum levels returned almost to the initial values, remaining like that until the end of the observation period (Figure 2).

3) *The serum proteins* were notably influenced by the drug; *the total proteins* had remained stable at or near the initial value, until the 43rd day, following which a sudden marked decrease was noted. *Albumin* showed a tendency to increase until the 43rd day, and thereafter, like the total proteins, they underwent a marked decrease. The mean values of the *total globulin* consistently decreased until the 73rd day; consequently, the A/G ration, by the 43rd day, increases and tends to reach the value of 1, thereafter, it shows a tendency to decrease again. As for

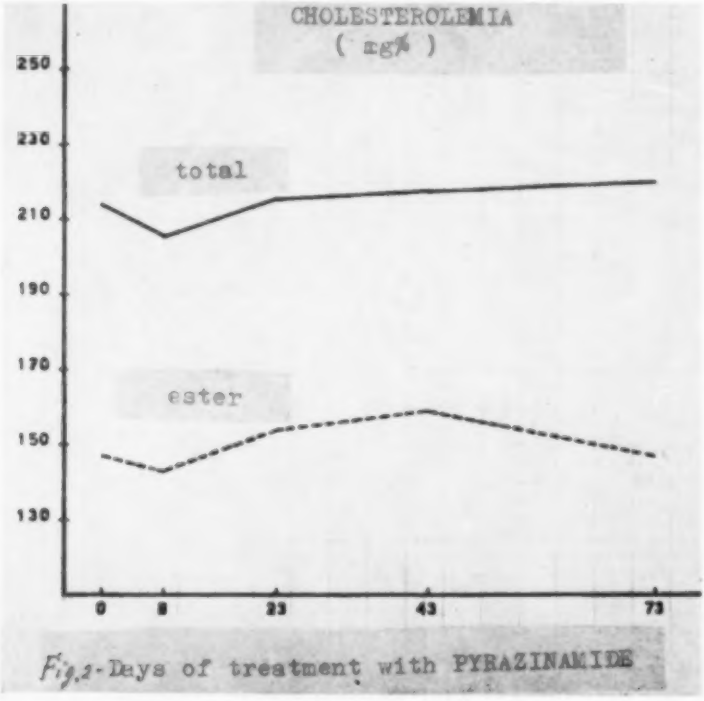

FIGURE 2

the individual *globulin fractions*, we observed that alpha 1, alpha 2 and gamma globulin tend to decrease, and beta globulin tends to increase; therefore, values in per cent of total globulin, which reveal the relations between the single globulin fractions, shows that while the decrease of alpha 1 and alpha 2 globulin has little meaning, the decrease of gamma globulin and the increase of beta globulin point out that the variations of these two fractions are more marked.

The *plasma fibrinogen* is but slightly influenced until the 23rd day of therapy; thereafter, it increases rapidly, presenting at the 73rd day of treatment mean values much higher than the initial ones (Figure 3).

4) *The prothrombin time*, after a marked increase within the first week, keeps lengthening more slowly until the 73rd day, and during the entire period, values are notably increased in relation to the starting ones (Figure 4).

5) *Urine 17-ketosteroid*. Within the first week of treatment, a sudden fall is noted, nearly exclusively in the male patients, and precisely for the same period wherein the increase of P.B.I. occurs (Figure 5).

6) *The peripheral blood counts* presented slight modifications of the

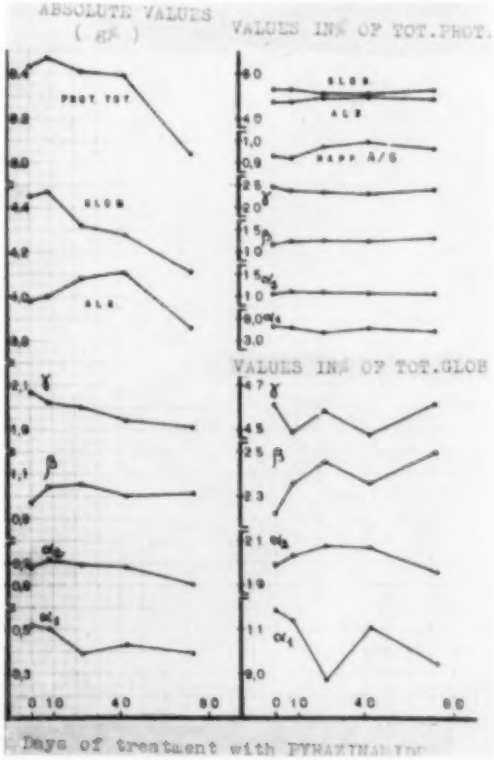

FIGURE 3

red series. Platelets showed a marked tendency to decrease, reaching the minimal level at the 43rd day. *The white series* presented a progressive leukopenia which, on the 73rd day, reached a mean value of 4.900. *Leukocytes* were slightly modified.

7) *The plasma lipasic power* presented some initial decrease, as occurred with INH, and thereafter it tends to reach a value corresponding to the clinical result (Figure 6).

8) *Specific proteases of defence in urine* presented a frequent initial decrease, forming then a descending curve that is very similar to that obtained during INH therapy (Figure 6).

9) In 15 out of the 30 subjects, the behavior of the Middlebrook-Dubos reaction and of phagocytosis was studied; no significant derivations were noted in the former, while phagocytosis showed a progressive decrease in cases with a favorable course.

The clinical and functional behavior of the liver, on the basis of our

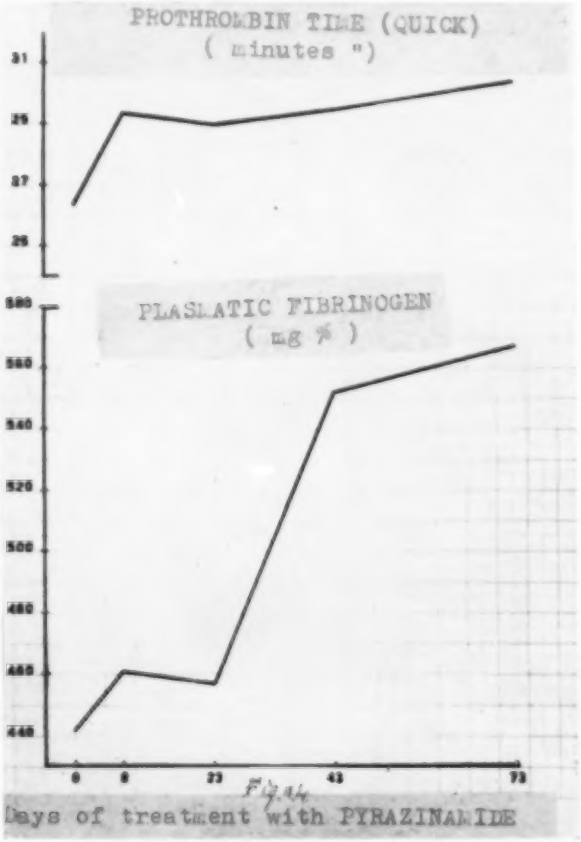

FIGURE 4

studies, showed *an exacerbation or the appearance of dyspepsia* in 1/3 of the cases; furthermore, *hepatic dysfunction is more frequently noted in subjects with preexisting hepatic disease and in those with no favorable results from therapy. According to the results of the laboratory tests done for evaluation of liver function, an evident agreement with the clinical observations is noted.*

In concluding, we can say that pyrazinamide therapy has resulted in subjective improvement of a good number of patients, at least for the first 40-50 days of therapy. This is important when considering that many of these patients were affected by chronic disease and had failed to show satisfactory improvement on other well known chemotherapeutic

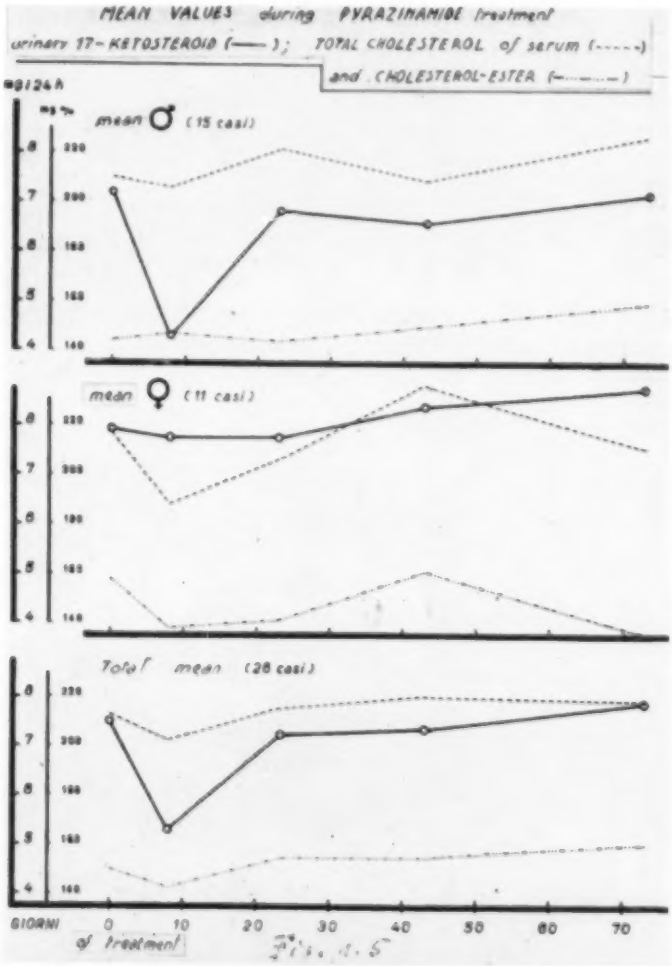

FIGURE 5

agents, because of intolerance or resistance. In modification of the above, we have not always observed roentgenographic improvement corresponding to the clinical state. In only seven cases were beneficial variations observed. From the point of view of complicating phenomena, two cases having jaundice and arthralgic episodes (these last being only transient) have to be mentioned.

In consideration of these observations, we can suggest that pyrazinamide should be utilized in the therapy of pulmonary tuberculosis only after the employment of more effective and less toxic agents; furthermore, the treatment period should not be too long (a maximum of 40-50 days) with the possibility of reinstating the administration in the interval of therapeutic regimens executed with other antituberculosis drugs. We do not have sufficient experience of treatment with pyrazinamide of cases of recent pulmonary tuberculosis, as have been reported in the American literature, and in the Italian literature by Daddi. It might be postulated that, in such conditions, therapy with pyrazinamide of short duration, eventually combined with isoniazid, could develop a remarkable therapeutic action, even if the toxic effects on the parenchyma of the liver are added.

At the present time, however, we do not believe it worthwhile to substitute this new antituberculosis agent in the place of combined therapy

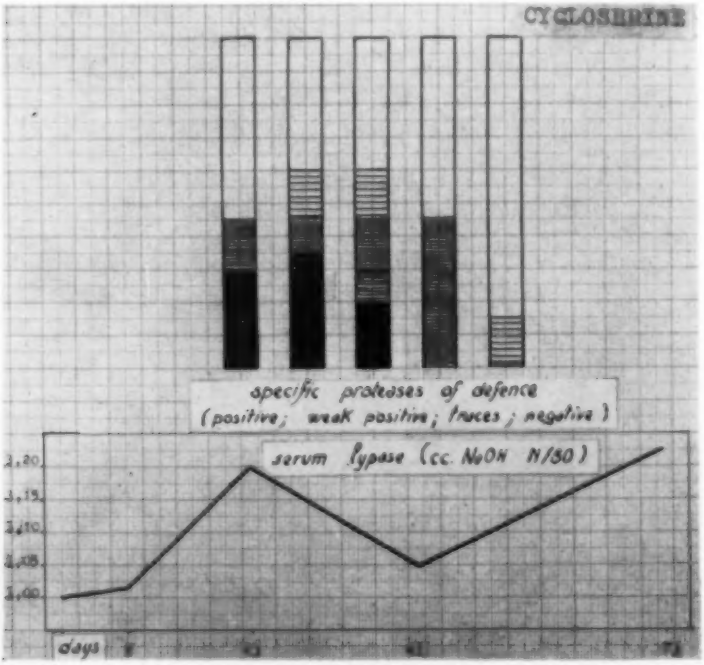

FIGURE 6

with streptomycin and isoniazid. This latter, in our opinion, remains the principal therapeutic method in the treatment of the incipient active post-primary tuberculosis.

Cycloserine

Our experience with this new antibiotic (supplied through the courtesy of Lilly, Merck, and Pfizer firms) is based on eight months of clinical observations on a total series of 88 patients. Sixty patients were treated with cycloserine alone (50 received a dose of 1 gr./daily, and ten 1.5 gr./daily; 26 had combined therapy of cycloserine (0.50 gr./daily) and isoniazid (300-400 mgr./daily); one cycloserine (0.50 gr./daily) and streptomycin (1 gr./daily) and one with cycloserine (0.50 gr./daily) and PAS (6 gr./daily). In the first group of 31 patients, (see table) the drug was administered in the dose of 1 gram daily (subdivided into four equal doses) starting on the first day, while in the other groups treated, this dosage level was reached gradually.

The clinical forms at the start of the therapy could be distinguished as follows: eight cases of pulmonary tuberculosis of early exudative and moderately advanced types (from one to five months of clinical evolution) with the clinical picture of early lobar infiltration or localized tuberculosis. Four were not treated with common anti-tuberculosis chemoantibiotics and four were treated with modest doses of streptomycin and isoniazid.

Five patients with exudative pulmonary tuberculosis of recent onset, moderately advanced, presenting a picture of confluent caseous extensive bronchopneumonia.

Ten cases of pulmonary tuberculosis, mainly exudative or miliary, moderately advanced, that in the course of chronic pulmonary tuberculosis or breakdown of old infiltrations or lobar disease.

Two cases of chronic disseminated miliary tuberculosis (cold miliary) resistant to the common antituberculosis chemoantibiotics;

Two cases of chronic metapneumothoracic empyema, combined and fistulized.

Six cases of chronic fibro-ulcerous or ulcero-caseous pulmonary tuberculosis, limited or extensive.

On the whole, therefore, we have treated 23 patients presenting with disease either advanced in the primary state or that occurring secondary in the course of a chronic illness, and 65 chronic forms.

The clinical and pertinent laboratory results have been collected in a table. Only in the first 31 cases therapy was terminated after 15 days (one case) to five months (Table II).

A) *From the clinical point of view*, the antibiotic, during the first phase of the therapeutic regimen, induced an improvement of the cenesthesia with remarkable decrease of coughing and expectoration, where they were present, and disappearance or decrease of fever in at least two-thirds of the treated cases.

For the first ten days of treatment, in about half of the cases a slight transient weight loss was observed with subsequent return to normal.

TABLE II

Clinical and Laboratory Data	Prior to Cycloserine Treatment		Number of Cases	After Cycloserine Treatment		Number of Cases
General conditions (cenesthesia, forces appetite, dynamism, toxiemic status)	Good Mediocre Decayed		7 13 11	Improved Unchanged Worse		17 10 4
Local conditions — Clinical Report				Improved Unchanged Worse Deaths		21 6 2 2
Local conditions — RX				Slightly improved Improved Unchanged Worse Cavity regression		6 15 6 4 7
Fever temperature	Present Absent		13 18	Appeared Disappeared Decreased Unchanged (where it was absent)		2 8 3 11
Coughing and expectoration	Abundant Scarce Absent		9 22 0	Increased Unchanged Decreased or disappeared		0 11 20
Tubercle bacilli research in the expectoration	Positive	direct on culture	26 27	Positive	direct on culture	13 16
	Negative	direct on culture	5 4	Negative	direct on culture	18 15
Weight				Increased Unchanged Decreased		19 8 4
S. R.				Increased Unchanged Decreased		3 6 22
Toxic and Allergic phenomena				Urticaria eruction Transient Art. Hypot. Drowsiness and Adynamia (within the first week of therapy) Convulsive crises Fever reactions (within the first week of therapy)		2 11 12 3 9
Glycemia				Unchanged		
Azotemia				Unchanged		
Urinary findings				Unchanged		

Some patients gained weight, and after a seven month period of observation, this was true for 62 per cent of the cases. Examination of the lungs showed a marked decrease of rales in 17 cases from the onset of therapy; in two, after one month of therapy, rales were again noted in the same site, but they were less prominent than before and shortly thereafter were not detectable on auscultation. After eight months of therapy, the clinical findings were improved in 21 cases and unchanged or worsened in the others. Two patients died, one after two months, the other after 27 days of therapy. In both cases, a form of chronic pulmonary tuberculosis, far advanced, was present with accompanying hemoptysis.

B) *The roentgenographic picture* was improved in 21 subjects (67 per cent). Evident with regression of wide exudative or miliary processes and the reduction or disappearance of pulmonary cavities in eleven cases (36 per cent) was noted.

We do not know if this disappearance will be temporary or permanent because of the short time that elapsed from the cessation of therapy (one to five months). In one case, a relapse was observed; however, after the reinstitution of therapy, regression of the pulmonary lesions was observed.

As for the clinical forms, we noted that the tuberculous processes, moderately advanced and severe, clinically primary or secondary in the course of a chronic pulmonary phthisis, had greater beneficial effects from the therapeutic action of the drug than did the chronic forms. In fact, out of nine patients who have completed therapy, seven showed regression or clinical stabilization of the morbid process.

However, in regard to the 18 cases of chronic or hyperchronic phthisis, resistant to the other antibiotics, we observed remarkable improvements with regression of old cavities in four patients. Six showed improvement of a slight degree, four were unchanged, two have become worse, and two have died.

In one case of chronic miliary tuberculosis, a striking and apparently definitive result was obtained. It was the problem of a subject already treated intensively with streptomycin and isoniazid, but without final success. Cycloserine therapy resulted in total reabsorption of the miliary foci and recovery of the concomitant laryngitis. In the other case, the result was poor.

In the empyema case treated, we did not observe any favorable result. More particular clinical details will be given in a few months when therapy in the remaining cases will be completed. At this time, we feel we will be able to support our observations by the results of one year of clinical study.

C) *From the bacteriologic point of view,* it is possible to state that following the first month of therapy, about one half of the patients became negative on direct examination. This finding remained constant and at the end of the eighth month of therapy, of the 26 patients positive for tubercle bacilli initially, 13 became negative on direct examination,

and of the 27 positive for tubercle bacilli on culturing, eleven have become negative (40 per cent).

D) *Collateral negative phenomena* were nearly of a slight degree and of five types:

1. In two cases, an *urticaria* was noted after about 20 days of therapy, with complete disappearance on discontinuing therapy.

2. In eleven cases, during the first 15-20 days of treatment, a minimal arterial hypotension was noted. This disappeared spontaneously with no interruption of therapy.

3. In twelve cases, drowsiness, followed by cephalgia, adinamia, and psychia depression had appeared with the first 48 hours. These symptoms disappeared after one-two weeks, cycloserine administration continuing uninterrupted.

4. In nine patients, a sudden rise of the fever was noted within the first 48 hours and this persisted for two to four days. This secondary rise probably occurred secondary to the reabsorption of tuberculin products coming from the bacillary bodies or from the products of tissue degeneration within the lesions. This mechanism is thought to be similar to the phenomenon of the immunological crisis described by E. Morelli and G. Daddi at the very beginning of therapy with isoniazid.

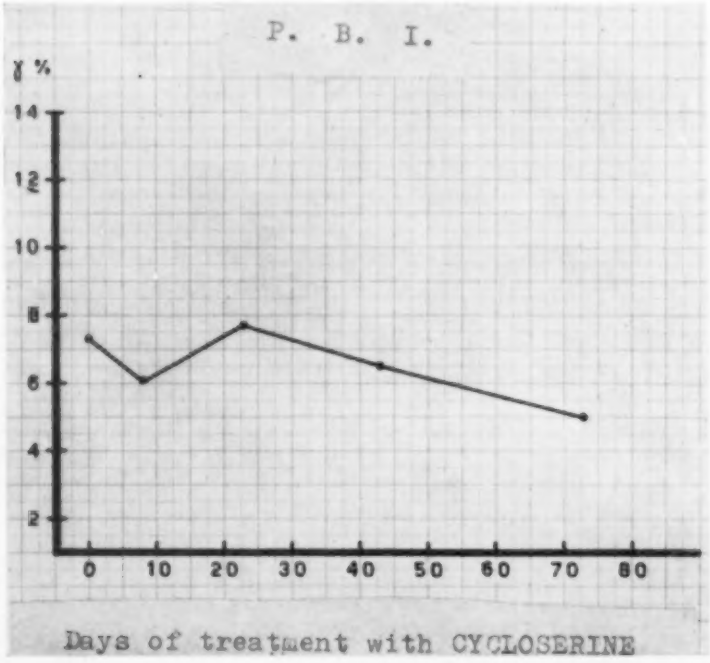

FIGURE 7

5. In three cases, severe side effects related to involvement of the nervous system were observed, manifested by periods of strong psychomotor agitation, alternating with periods of drowsiness and followed by schizoid phenomena in one case. One patient attempted suicide. In two cases, it has been possible to continue therapy following an interrupted period of one to two weeks and a good clinical result was obtained. In the third case, the therapy was completely stopped. Involvement of the C.N.S. is less frequent, when the dosage is carefully regulated and a more selective choice of patients is effected.

In addition to the above mentioned phenomena, symptoms were noted in two patients at about the 45th day of therapy and a questionable relationship to cycloserine is postulated. These symptoms were characterized by a sense of thoracic constriction, dyspnea at minimal effort, and without objective evidence of impaired cardiorespiratory function or bronchospasm. These symptoms disappeared spontaneously after two to three days, the interruption of cycloserine therapy not being necessary.

E) In four cases, noted reported in the above mentioned table, for which cycloserine was administered by endocavitary way (four women who had undergone a treatment of loboretraction according to the technique of Omodei Zorini, Bottari and Di Paola) the drug was introduced in the dose of 0.50 gr. divided into two daily doses and accompanied by endocavitary aspiration according to the method of Monaldi. No general

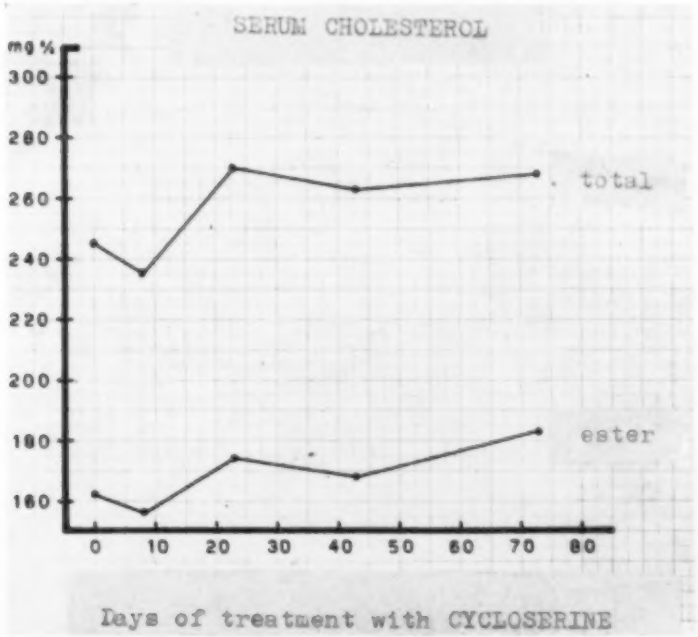

FIGURE 8

or local disturbances were noted and the endocavitary secretion became negative for tubercle bacilli after a therapeutic period of two to six weeks. In three patients, the so-treated cavitations were nearly completely eliminated, and in two of them, an apico-axillary thoracoplasty procedure was done.

In addition to routine clinical investigations, a number of biochemical, biologic, and hematologic examinations were carried out, the results of which we shall briefly report since this will be the first time some of the results will have appeared in the literature.

1) *The precipitable bound iodine*, after an initial decrease, showed a sudden increase at the 23rd day, subsequently falling below the starting values (Figure 7).

2) *Cholesterol and cholesterol-esters* follow essentially the behaviour of P.B.I., remaining however slightly higher than the starting values by the end of the observation period (Figure 8).

3) *Serum proteins* showed marked variations: the *total proteins* in-

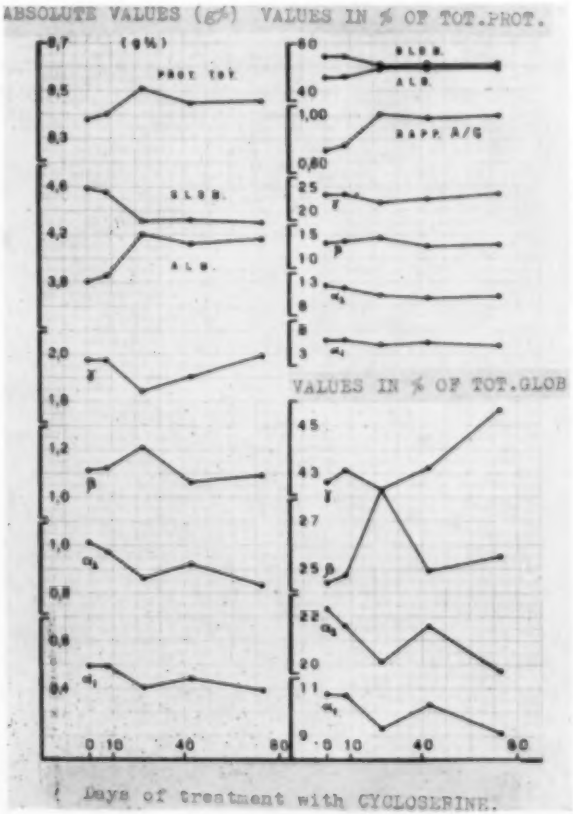

FIGURE 9

creased gradually until the 43rd day, at which time a slight decrease was noted, the serum levels remaining above the initial values; however, *total globulin* underwent a marked decrease until the 73rd day of therapy; in the meantime, *albumin* increased considerably until the end of the therapy, so that A/G ratio previously altered has returned to the initial values by the 23rd day and remains thus to the end of the observation period. As for the *globulin fractions*, a tendency to decrease is observed for all of them, with only an initial decrease noted for gamma globulin.

In evaluation of the respective globulin decrease in terms of percentage, it is readily deduced that the overall decrease is concerned especially with alpha 1 and with alpha 2 globulin (Figure 9); while gamma globulin clearly tends to increase with the time. The *plasma fibrinogen* presents a steady decrease from the beginning to the end of the observation period, behaving in the opposite manner observed during pyrazinamide therapy (Figure 10).

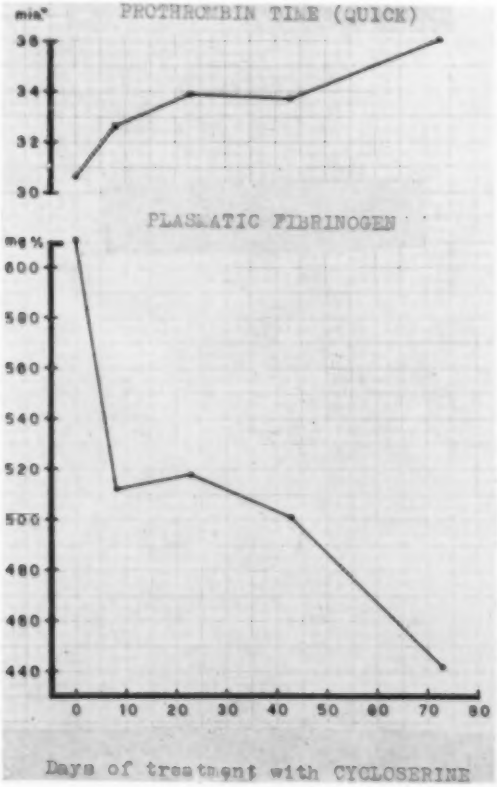

FIGURE 10

4) *The prothrombin time* from the beginning shows a prolongation which persists until the end of therapy (Figure 10).

5) *The Thorn index* showed a steady decrease over the entire observation period, of the number of circulating eosinophils of the uric acid/creatinin ratio, of azoturia. Also, urinary 17-ketosteroid were noted to have a tendency to decrease.

6) From the study of *the peripheral blood counts*, we have observed for both the white and the red series a slight increase of mean values.

7) *The plasma lipasic power* has progressively *increased* (Figure 11).

8) *Specific proteases of defense in urine* showed an initial increase; followed by a decrease, this pattern of behavior being opposite to that observed during pyrazinamide therapy (Figure 11).

As for clinical and functional liver behavior (Mariani), it is possible to state that contrary to what happened during the pyrazinamide therapy, cycloserine did not cause any toxic reactions to the liver, and furthermore, it behaved almost like a protective agent.

There were some subjects in whom evidence of severe liver dysfunction was not noted at the start of therapy, but in whom minimal alteration of liver function was present. In these cases, even these minimal signs of hepatic dysfunction diminished during the course of therapy. In other cases, demonstrating even more severe clinical evidence of hepatic dysfunction, further resolution was noted during therapy.

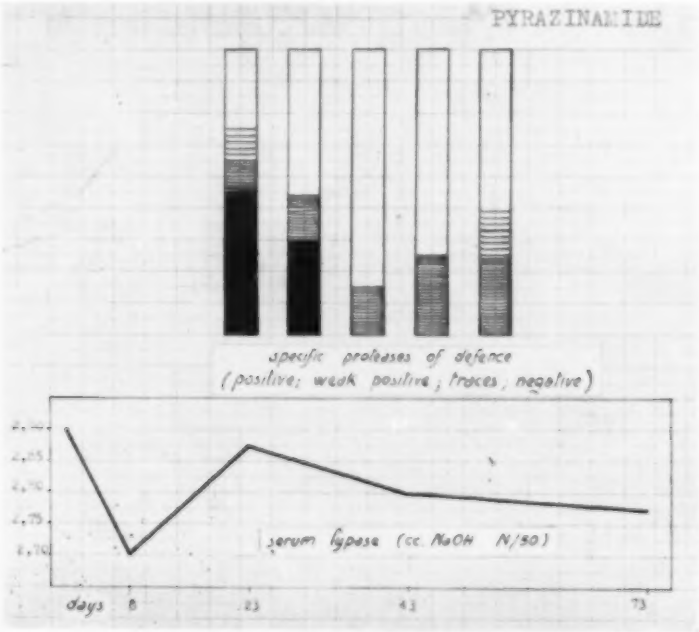

FIGURE 11

The graph based on mean values of the casuistry, clearly shows this behavior before, during, and at the end of therapy.

Clinical, subjective, and objective liver findings were in agreement with data given by the laboratory tests.

In conclusion, we can state that cycloserine has induced in two thirds of the treated patients an appreciable clinical improvement and significant modifications of the roentgenographic picture featured by cavity closure and regression of exudative and miliary foci in 36 per cent of patients. In about 40 per cent of subjects initially positive for tubercle bacilli, the sputum became negative on both direct smear and culture. Although we recognize that the number of cases included in this study is too small to make unequivocal deductions, nevertheless, after eight months of clinical observation, supported by a number of laboratory tests, it is possible to state that cycloserine is a new drug with definite therapeutic activity against human tuberculosis, showing marked therapeutic effects in recent forms, and a lesser degree of efficacy in a certain number of chronic cases which have become resistant to the well-known and widely used drugs.

SUMMARY

1. A series of clinical and biological investigations on pyrazinamide and cycloserine in the treatment of pulmonary tuberculosis are reported.

These investigations were accompanied by the following laboratory studies: serum electrophoresis, phagocytic index, precipitable bound iodine, adrenal cortical function, behavior of specific proteases of defense in urine, plasma lipasic power, serum cholesterol, serum bilirubin, plasma fibrinogen, prothrombin time, and finally with the serolability tests and the charge tests of liver function.

Pyrazinamide showed a favorable action on tuberculous lesions in a limited number of cases and for a short duration, not exceeding 35-40 days of therapy, following which toxic phenomena were observed, predominantly hepatic. The laboratory tests in this subsequent period of study showed increasing variance from normal values, with an increase of the precipitable bound iodine and a dissociation between the globulin with an increase in the beta and a decrease in the gamma fraction.

2. Cycloserine, on the basis of our studies, was thought to be a more patient antibiotic, manifested by definite improvement in the x-rays of both fresh exudative cases, as well as in cases of chronic cavitary disease, some of these being resistant to the usual therapeutic measures, with appreciable regression of the far advanced cavitations, and conversion of a positive sputum to negative in both types of cases. Its toxic action on the central nervous system is not frequent and does not usually interfere with the continuance of therapy. The laboratory tests have generally shown normal values even after the second and third month of therapy with the precipitable protein bound iodine, serum proteins, and particularly beta gamma globulin, plasma fibrinogen, prothrombin time, plasma lipasic power, specific proteases of defense in urine, and the charge tests for liver function, presenting a behavior opposite to that of pyrazinamide.

RESUMEN

1. Se relatan una serie de investigaciones clínicas y biológicas sobre pirazinamida y cicloserina en el tratamiento de la tuberculosis pulmonar.

Estas investigaciones se acompañaron de los siguientes estudios de laboratorio: electroforesis del suero, índice fagocitario, yodo compuesto precipitable, función córtico suprarrenal, suerte de las proteasas específicas de defensa en la orina, poder lipásico del plasma, colesterol sanguíneo, bilirrubina en el suero, fibrinógeno del plasma, tiempo de proptrombina, y finalmente, pruebas de serolabilidad y las pruebas de carga de la función hepática.

La pirazinamida mostró una acción favorable sobre las lesiones tuberculosas en un número limitado de casos y por corto tiempo que no sobrepasó de 35-50 días de tratamiento siguiendo fenómenos tóxicos con predominio de los hepáticos. Las pruebas de laboratorio en este subsecuente período de estudio, mostraron variación creciente desde los valores normales con un aumento del yodo ligado precipitable y una disociación entre la globulina con un aumento de la beta y disminución de la fracción gama.

2. La cicloserina, basándonos en nuestros estudios, se encontró más potente como antibiótico según el cambio manifiesto a los rayos X tanto en los casos de lesiones exudativas recientes, como en los casos de cavitarios crónicos, algunos de estos aún siendo resistentes a los recursos terapéuticos habituales con una regresión apreciable de las excavaciones en los muy avanzados y conversión de positivos a negativos en esputos en ambos tipos de enfermedad. Su acción tóxica sobre el sistema nervioso central no es frecuente y generalmente no interfiere con la continuación del tratamiento. Las pruebas de laboratorio generalmente han mostrado valores normales aún después del segundo y tercer mes de tratamiento con todas las pruebas mencionadas al principio de este resumen comportándose de manera opuesta a la pirazinamida.

RESUME

Les auteurs rapportent une série d'investigations cliniques et biologiques sur le traitement de la tuberculose pulmonaire par la pyrazinamide et la cyclosérine.

Ces investigations étaient accompagnées des études de laboratoire suivantes: électrophorèse du sérum, index phagocytique, étude de la précipitation iodée, fonction adréno-corticale, comportement des protéases spécifiques de défense dans les urines, pouvoir lipasique du plasma, dosage du cholestérol, de bilirubine, du fibrogène plasmatique, temps d'action de la prothrombine, et enfin tests d'instabilité du sérum, et tests de charge de la fonction hépatique.

La pyrazinamide montra une action favorable sur les lésions tuberculeuses dans un nombre limité de cas, et pendant un temps court n'excédant pas 35 à 50 jours de traitement, après cela des phénomènes toxiques, principalement hépatiques, furent observés. Les tests de laboratoire dans cette phase postérieure de l'étude montrèrent des taux en augmentation par rapport aux valeurs normales, avec un accroissement du pouvoir précipi-

tant de l'iode et une dissociation des globulines avec une augmentation de la beta globuline et une diminution de la fraction gamma.

2. D'après ces études, la cyclosérine peut être tenue pour un antibiotique plus efficace, ceci étant démontré par l'amélioration radiologique incontestable, aussi bien des cas exsudatifs récents que des cas d'affections cavitaire chronique; quelques-une de ces cas étaient résistants aux moyes thérapeutiques habituels et il y eut une régression appréciable des processus cavitaires très avancés, et la négativation bactériologique des expectorations dans les deux exemples de ces cas. Son action toxique sur le système nerveux central n'est pas fréquente, et ne trouble généralement pas la poursuite du traitement. Les tests de laboratoire ont montré des valeurs généralement normales, même après le deuxième et le troisième mois de traitement selon le test de précipitation iodée, le test des protéines sériques, et surtout le test à la globuline beta et gamma, le fibrinogène plasmatique, le temps de prothrombine, le pouvoir lipasique du plasma, les protéases spécifiques de défense dans les urines, et les tests de charge de la fonction hépatique, qui présentèrent un comportement opposé à celui des tests obtenus au cours du traitement par la pyrazinamide.

ZUSAMMENFASSUNG

1. Bericht über eine Reihe von klinischen und biologischen Untersuchungen über Pyrazinamid und Cycloserin bei der Behandlung der Lungentuberkulose.

Diese Untersuchungen erfolgten in Verbindung mit folgenden Laboratoriumsuntersuchungen: Serum-Elektrophorese, Phagocyten-Index, ausfällbares gebundenes Jod, Nebennierenrinden-Funktion, Verhalten von spezifischen Abwehrproteasen im Urin, Plasma-Lipase-Vermögen, Serum-Cholesterin, Serum-Bilirubin, Plasma-Fibrinogen, Prothrombin-Zeit und schliesslich Serum-Labilitäts-Prüfungen und die Belastungsteste der Leberfunktion.

Pyrazinamid zeigte einen günstigen Einfluss auf tuberkulöse Herde in einer begrenzten Zahl von Fällen und für eine kurze Dauer, die keine 35-50 Behandlungstage überschritt und im Anschluss daran toxische Phänomene zeitigte, vorwiegend von Seiten der Leber. Die Laboratoriumsuntersuchungen während dieser anschliessunden Prüfungsperiode zeigten eine zunehmende Abweichung von normalen Werten mit Anstieg des ausfällbaren gebundenen Jods und einer Dissociation innerhalb der Globuline mit einem Anstieg in der Beta- und einer Abnahme in der Gamma-Fraktion.

2. Von Cycloserin wurde auf Grund unserer Untersuchungen angenommen, dass es ein vorzüglicheres Antibioticum sei, wie dies zum Ausdruck kommt durch definitive Besserung in den Röntgenbildern sowohl von frischen exsudativen Fällen, als auch von Fällen mit chronisch-cavernöser Krankheitsform, von denen einige resistent waren gegenüber den gewöhnlichen therapeutischen Massnahmen mit merklicher Rückbildung der weit fortgeschrittenen Cavernisierungen und Erlangung von Bazillenfreiheit bei beiden Krankheitsformen. Sein toxischer Einfluss auf das Zentralnervensystem ist nicht häufig und hindert für gewöhnlich nicht die Fort-

setzung der Therapie. Die Laboratoriumsuntersuchungen zeigten im Allgemeinen normale Werte, sogar nach dem 2. und 3. Behandlungsmonat hinsichtlich des ausfällbaren am Eiweiss gebundenen Jods, der Serum-Proteine und besonders Beta- und Gammaglobulin, Plasma-Fibrinogen, Prothrombin-Zeit, Plasma-Lipase-Vermögen, spezifischer Abwehrproteasen im Urin und den Belastungsproben für die Leberfunktion—ein Verhalten, das demjenigen bei Pprazinamid sich als entgegengesetzt erweist.

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Circumscribed Intrapulmonary Hematoma Presenting as a "Coin" Lesion

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In recent years the problem of solitary circumscribed pulmonary nodules has attracted much attention in the medical literature. The difficulties involved in establishing an accurate diagnosis in cases of this kind are well recognized and are usually resolved by resort to exploratory thoracotomy and excision of the lesion. That this approach to the problem is rational and well founded is amply substantiated by the many excellent reviews on the subject which have established an incidence of malignancy in such cases varying from approximately 7 to 74 per cent and averaging about 37 per cent.[1-9] The major portion of this group is, of course, comprised by primary bronchogenic carcinoma, while metastatic tumors and other primary malignant diseases such as bronchial adenoma, sarcoma or lymphoblastoma make up a much smaller component. Non-malignant lesions which most commonly present as isolated pulmonary nodules are tuberculomas, granulomas of nonspecific origin, hamartomas, histoplasmomas and coccidioidomas. In addition to the above disorders there is a great variety of less common and even rare conditions which may assume the form of "coin" lesions and with which the physician must be familiar if he is even to consider the correct diagnosis prior to surgical exploration of the chest. To but mention some of these diseases—chronic organized pneumonitis, lung abscess, bronchogenic cyst, pleural mesothelioma, lipoid granuloma, neurofibroma, pulmonary infarct, encapsulated pleural effusion or empyema, blastomycosis, cryptococcosis, hemangioma, hydatid cyst, fibrin body and brucellosis may all appear as solitary circumscribed pulmonary nodules.

The following report purports to add to this list another condition which hitherto has received but little attention, that is, intrapulmonary hematoma.

Persistent, circumscribed, intrapulmonary hematomas must be either extremely rare in occurrence or generally unrecognized if one can judge from the few cases which have appeared in the literature.

Although a number of authors[10-13] have briefly described or referred to hematoma formation in the lung, the roentgenographic changes produced by these lesions have been variously indicated as "spindle shaped"[10, 13] or "ill defined"[11, 12] and have not presented the sharply circumscribed, round or oval appearance of the so-called "coin" lesion. Only the three cases reported by Salyer, Blake and Forsee[14] and the single

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case mentioned by Condon[15] fall into this category. To this group a fifth such case is added in the following report.

Case Report: G. C. H., a 60 year old white male cook, was admitted to the hospital on May 5, 1954, for the treatment of an inguinal hernia. A routine admission roentgenogram of the chest disclosed the presence of a sharply outlined circular density in the right lower lung field and this lesion then became the object of major diagnostic interest. History disclosed that the patient had enjoyed relatively good health until December, 1949, when he developed the onset of sudden severe pain in the low back region. He was admitted to the hospital at that time, where roentgenograms of the skeletal system disclosed generalized demineralization associated with collapse of the first lumbar vertebra together with anterior wedging of several thoracic vertebrae. Roentgenographic examination of the chest disclosed a healing fracture of the anterior aspect of the right seventh rib but no evidence of a parenchymal lesion. A diagnosis of multiple compression fractures of the vertebrae due to senile osteoporosis was established and he was discharged in January, 1950, after satisfactory response to rest and the application of a back brace. In August, 1953, he fell and sustained a fracture of the right hip. He was treated at another hospital and apparently made an uneventful recovery. Thereafter he did well until February, 1954, when he developed a "cold" associated with nonproductive cough, fever and severe pain in the right posterior chest. Treatment at a local outpatient clinic resulted in prompt improvement, although the thoracic pain persisted for three weeks. An x-ray film of the chest on February 16, 1954, disclosed no abnormality other than "bilateral emphysema." In the latter part of March, 1954, he fell and struck the right side of his thorax. Soreness at the site of injury gradually subsided in approximately two weeks. During this period he complained of mild exertional dyspnea and noted an alleged decline in weight from 165 to 138 pounds, but he sought no further medical attention until the present admission when he entered the hospital for the aforementioned hernia repair.

Physical Examination: On admission to the hospital he appeared to be well developed and well nourished. He was mentally alert and showed no evidence of acute illness. Temperature 98.0°, pulse 84, blood pressure 160/110. The thorax appeared to be narrowed and exhibited an increased anterior posterior diameter. Breath sounds were generally diminished in intensity and the percussion note was hyperresonant over both lung fields. Other physical findings included evidence of generalized arteriosclerosis, prostatic hypertrophy, bilateral varicosities of the lower extremities, prominent kyphosis of the dorsal spine and a reducible, indirect, left inguinal hernia.

Laboratory and X-ray Film Findings: Roentgenograms of the chest disclosed a sharply circumscribed rounded lesion in the lower lobe of the right lung (Figures 1, 2, and 3). The shadow measured 3.5×4.0 cm. in diameter and appeared to be homogenous but of low density. Although the lesion apparently touched the pleura posteriorly it seemed to be entirely located within the lung parenchyma. The remainder of the lung fields showed evidence of emphysematous changes. Healing fractures of the right seventh posterior rib and the posterior portions of the left eighth and ninth ribs were noted. A complete bone survey disclosed marked generalized demineralization throughout the skeletal system. There had been some progression of the multiple vertebral compressions since previous films of December, 1949. An intravenous pyelogram, a gastrointestinal series and a barium enema were negative. Tuberculin skin test (PPD) gave a positive reaction while testing with coccidioidin and histoplasmin was negative. Sulkowitch's test disclosed no increase in urinary calcium. Serum calcium 10.5 mg. per cent, serum phosphorous 3.5 mg. per cent, alkaline phosphatase 6.0 Bodansky units, acid phosphatase .07 K. A. units. Sputum, blood count, urinalysis, liver function studies and stool examinations were negative.

Course in Hospital: When diagnostic studies failed to clarify the etiology of the pulmonary nodule, the right thorax was entered through the bed of the excised seventh rib on June 2, 1954. A "cystic" lesion,

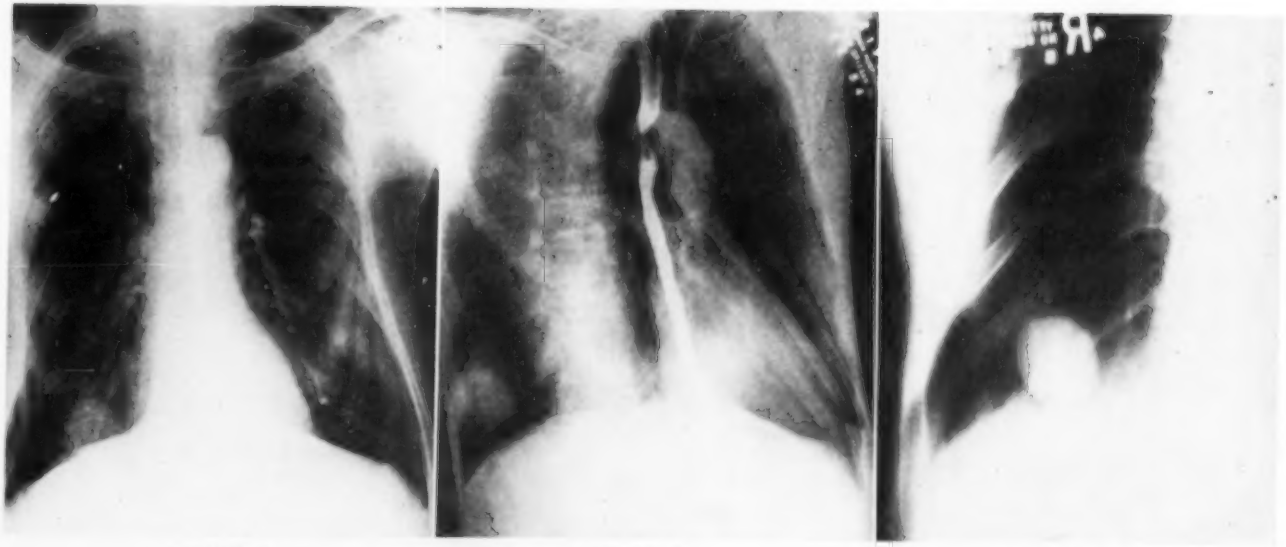

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Erect postero-anterior roentgenogram of the chest showing a sharply outlined circular density in the right lower lung.—*Figure 2:* Right anterior oblique roentgenogram of the chest illustrating the posterior location of the lesion. Although it touches the chest wall it appears to be completely located within the lung parenchyma.—*Figure 3:* Body section roentgenogram illustrating the discrete outlines and homogeneous character of the lesion.

the size of a "golf ball" was encountered in the posterior aspect of the right lower lobe. Approximately one third of the lesion protruded subpleurally, while the remainder was buried in the parenchyma of the lung. The specimen, removed by "snip" resection, consisted of fluctuant mass which, when opened, was found to be cystic and contained approximately 6 cc. of dark red blood with some irregular small clots. When the blood was washed away the lining of the cyst was white and finely granular with some red fibrin strands attached. The wall of the cyst was less than 1 mm. in thickness; it appeared dense and fibrous. Microscopic examination disclosed a well-organized cyst wall surrounded by compressed lung parenchyma externally. Fragments of fibrin and degenerating blood were attached to the inner cyst wall (Figure 4). The pathological diagnosis was hemorrhagic cyst, post-traumatic (organized pulmonary hematoma). Microscopic study of the resected rib disclosed osteoporosis and a healing fracture.

The postoperative course was uneventful. On June 29, 1954, a left inguinal hernioplasty was carried out and on October 5, 1954, he underwent transurethral resection of the prostate. On October 20, 1954, he was discharged from the hospital. He was last seen when rehospitalized following a fall which caused severe pain in the lower back. This com-

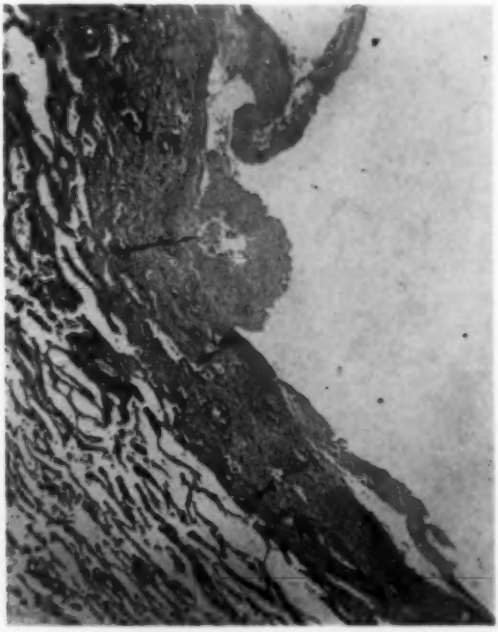

FIGURE 4: Photomicrograph of a section of the wall of the hematoma demonstrating its well organized fibrotic character. Shreds of fibrin can be seen on the inner surface of the cyst while compressed lung tissue is visualized externally.

plaint responded to rest and the application of a lumbosacral corset. X ray films of the chest were unchanged and he was discharged on January 19, 1956.

Discussion

Results of trauma to the lung or pleura are usually easily recognized. A clear-cut history of injury, either penetrating or nonpenetrating, is almost always obtained and physical evidence of trauma is seen in the form of rib fractures or contusions of the chest wall. If these findings are further associated with the typical roentgenographic appearance of hemothorax, pneumothorax or pneumohemothorax, it is easy to ascertain that injury to the pleura has occurred.

Violence to the chest may also injure the pulmonary parenchyma without apparent evidence of pleural perforation. Roentgenographic findings are less characteristic, in such cases, but usually reflect the results of hemorrhage and edema within the lung substance. Areas of diffuse infiltration or consolidation are seen, sometimes associated with an atelectatic component resulting from intrabronchial bleeding. The nature of these findings is further clarified by their tendency toward prompt regression during a period of a week or more.

Where the intrapulmonary bleeding is localized and becomes sharply circumscribed into the form of a solitary hematoma the diagnosis becomes less certain, since this type of lesion may be clinically indistinguishable from a primary bronchogenic carcinoma or any other condition which can assume the appearance of a "coin" lesion. In spite of a history of trauma, the presence of rib fractures or evidence of other injury to the chest, the physician is now confronted by an indeterminate pulmonary lesion, the exact nature of which can be established only by resort to exploratory thoracotomy. This was the situation in the cases reported by Salyer et al[14] and in the patient we described.

Since all of the sharply circumscribed intrapulmonary hematomas thus far reported have been surgically excised, little is known of their ultimate fate. In describing poorly defined hematomas of the lung secondary to blast or nonpenetrating injury McGrigor and Samuel[12] state that resolution of the lesion may take as long as six to eight weeks. Blair[11] indicates a similar course for hematomas of this type. In 1950 Welkind[13] reported what was probably the first case of a sharply circumscribed pulmonary hematoma to appear in the medical literature. The lesion was described as "a tumor-like shadow consisting of two spindle masses which fused at their axillary ends." Resolution gradually took place over a period of 13 months, leaving two persistent linear scars. The author felt it to be "inconceivable that a simple hematoma would take 13 months completely to resorb," and postulated that the lesion was associated with an element of infarction or that it was possible "some sort of thick capsule formed around the clotted blood, retarding the resolution." He closed his paper with the prediction that final solution of the problem would come only from postmortem studies of hematomas months or years after injury. In 1953 Salyer et al[14]

provided such a solution when they removed three localized pulmonary hematomas by surgical resection. Two of these lesions were described as cystic cavities filled with clotted blood. Similar pathological changes were, of course, encountered in our own case. As Welkind[13] postulated, it is undoubtedly the cyst formation which accounts for the persistent nature of these lesions. Just how long a well organized encapsulated hematoma might remain unchanged within the lung is still a matter for speculation. Although our patient was observed for only one month prior to resection, in two of Salyer's[14] cases the lesions exhibited no tendency toward resolution over periods of eight and 12 weeks. In Salyer's[14] third patient the hematoma showed no change in size during a period of three and a half months, but a bronchial communication developed and the cyst underwent partial evacuation of its contents, leading the authors to speculate on the dangers of chronic suppuration or frank abscess formation. This complication indicates that at least some of these lesions may be regarded as potentially dangerous to the patient. However, it seems likely that in most instances the hematoma would exhibit gradual resolution, as in Welkind's[13] case, while in others it would persist for even longer periods, eventually undergoing fibrosis or perhaps calcification.

SUMMARY

1. A case of solitary, sharply circumscribed, intrapulmonary hematoma following non-penetrating injury of the chest is reported. The hematoma presented as a "coin" lesion clinically indistinguishable from a peripheral bronchogenic carcinoma or other conditions known to produce discrete pulmonary nodules.

2. The shape, the sharp outline and the tendency of these lesions to persist unchanged within the lung for long periods can apparently be ascribed to the formation of a fibrotic cyst wall around the hematoma.

3. Pulmonary hematomas of this type appear to be distinctly rare, but should be considered in the differential diagnosis of isolated discrete nodules of the lung, particularly if there is a prior history of chest trauma or evidence of rib fracture. Even though the nature of such a lesion is suspected, exploratory thoracotomy will usually be required in order to establish the correct diagnosis.

RESUMEN

1. Se relata un caso de un hematoma después de una herida no penetrante de tórax, el que fué solitario, y bien circunscrito. Esehematoma revistió el aspecto de una lesión de las llamadas en "moneda," clínicamente indistinguible de un carcinoma bronquiogénico periférico o de otras afecciones que se sabe producen nódulos discretos en el pulmón.

2. La forma, el contorno limitado y la tendencia de estas lesiones a persistir sin cambios dentro del pulmón por largo tiempo, puede atribuirse a la formación de una pared de quiste fibroso alrededor.

3. Estos hematomas son raros pero deben tenerse presentes en el diag-

nóstico diferencial de los nódulos asilados y discretos del pulmón especialmente si hay antecedente de trauma del tórax o fractura de costilla.

Aunque la naturaleza de estos se sospeche la toracotomía exploradora se requerirá para aclarar el diagnóstico.

RESUME

1. Les auteurs rapportent un cas d'hématome intrapulmonaire isolé, très circonscrit, faisant suite à un traumatisme non pénétrant de la poitrine. L'hématome se présentait comme une lésion en "pièce de monnaie," qui ne pouvait pas se différencier d'un cancer bronchique péhiphérique ou d'autres états connus pour produire des nodules pulmonaires discrets.

2. La forme, le tracé précis, la tendance de ces lésions à persister sans changement à l'intérieur du poumon pendant de longues périodes, peuvent apparemment être attribuées à la formation d'une paroi fibro-kystique autour de l'hématome.

3. Les hématomes pulmonaires de ce type semblent être rares, mais devraient être pris en considération dans le diagnostic différentiel des nodules discrets isolés du poumon, particulièrement s'il y a auparavant une histoire de traumatisme thoracique ou la preuve d'une fracture de côte. Même quand on suspecte la nature d'une telle lésion, il sera généralement indiqué de pratiquer une thoracotomie exploratrice pour affirmer le véritable diagnostic.

ZUSAMMENFASSUNG

1. Bericht über einen Fall eines solitären, scharf umschriebenen intrapulmonalen Hämatoms im Anschluss an ein stumpfes Trauma des Brustkorbes. Das Hämatom stellt einen "Rand"—Herd dar und ist klinisch nicht zu unterscheiden von einem peripheren, bronchogenen Carcinom oder anderen Affektionen, von denen bekannt ist, dass sie zur Bildung von diskreten pulmonalen Knötchen führen.

2. Die Gestalt, die scharfe Begrenzung und die Tendenz dieser Herde, unverändert in der Lunge für lange Zeiträume bestehen zu bleiben, kann augenscheinlich die Bildung einer fibrotischen Cystenwand um das Hämatom herum zugeschrieben werden.

3. Pulmonale Hämatome dieses Types scheinen ausgeprochen selten zu sein; man muss sie jedoch in Erwägung ziehen bei der Differential-Diagnose isolierter diskreter Knotenbildungen der Lungen, besonders wenn in der Vorgeschichte ein Thorax-Trauma vorkommt, oder der Befund einer Rippenfraktur besteht. Aber selbst wenn man die Natur einer solchen Veränderung vermutet, wird eine diagnostische Thorakotomie für gewöhnlich notwendig sein, um eine genaue Diagnose sicher zu stellen.

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Pulmonary Tuberculosis and Peptic Ulcer*

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For several years we have been impressed by the increasing frequency of gastric symptoms in patients with pulmonary tuberculosis. The coexistence of this disease with peptic ulcer has been called to attention in Europe and in recent reports from the United States. Our observations are illustrated by the analysis of 27 cases of pulmonary tuberculosis at Worcester County Sanatorium in which peptic ulcer was demonstrated either before admission or during the course of hospitalization. Radiological proof of the ulcer is available in all cases. Ulcers associated with neoplasm were excluded from this series. The cases are divided into four categories.

In the interpretation of these figures we should remember that not until recently did we become fully alert to the problem and to the need for a more detailed investigation of the gastrointestinal system in tuberculous patients. In recent years we also had the opportunity to witness among our admissions the prevalence of tuberculosis in elderly men, a fact which was emphasized by the transfer of such patients from another hospital. Only three of the cases were women. The age of our patients at the time of admission ranged from 38 to 79 with an average of 55. The average age at the time of diagnosis was 50 for pulmonary tuberculosis and 48 for peptic ulcer. In one the tuberculosis was moderately advanced. All others had far advanced disease.

The first group includes 12 patients who developed tuberculosis after surgery for peptic ulcer. Nine had gastrectomy, total or subtotal, and two gastroenterostomy. The last one had "closure" of a gastric ulcer but required gastrojejunostomy at a later admission. The interval between abdominal surgery and onset of tuberculosis ranges widely from less than one year to 37 years. In case seven the sequence of events is difficult to determine since the patient's lung disease may well antedate his operations.

The second group is made up of four patients whose gastrointestinal symptoms appeared after surgical treatment of pulmonary tuberculosis by thoracoplasty. The interval between operation and discovery of the peptic ulcer varies from four months to seven years. In this group there were three duodenal and one gastric ulcers. These patients also received chemotherapy including oral PAS medication before the onset of abdominal symptoms. In case 13 a gastric ulcer developed in the wake of cortisone therapy for severe rheumatoid arthritis which complicated the tuberculosis.

The third group includes seven cases in which pulmonary tuberculosis preceded the onset of peptic ulcer. The latter was discovered at autopsy

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in three, with signs of recent hemorrhage in two. Six had received oral chemotherapy before the ulcer manifested itself. Case 21 had extensive thoracic surgery within six weeks before his death, and a peptic ulcer was found at autopsy. In three cases the ulcer was located in the stomach and in the other four in the duodenum.

In the four cases of the fourth group, as in the first, the ulcers, one gastric and three duodenal, preceded the onset of tuberculosis but the treatment was medical rather than surgical.

Discussion

In the past 10 years it has been commonly noted that an increasing number of patients admitted to tuberculosis hospitals showed the scar of previous gastrectomy. This observation coincides with a strikingly large proportion of patients who complain of "stomach upsets" or "heart burn" and are found to be victims of peptic ulcer. The literature now offers rather frequent reports which can generally be divided into two categories:

a. Pulmonary tuberculosis after gastrectomy for peptic ulcer.

French writers were the first to discuss this relationship. Isorni and associates[1] present 26 patients with gastrectomies among 742 admissions for pulmonary tuberculosis. Thirteen of these had no manifestation of tuberculosis before operation. The average interval between operation and the onset of pulmonary tuberculosis was three years. In the United States, Warthin[2] finds that 2 per cent of 356 gastrectomized patients developed active pulmonary tuberculosis. Allison[3] reports 21 cases of pulmonary tuberculosis following gastrectomy for peptic ulcer among

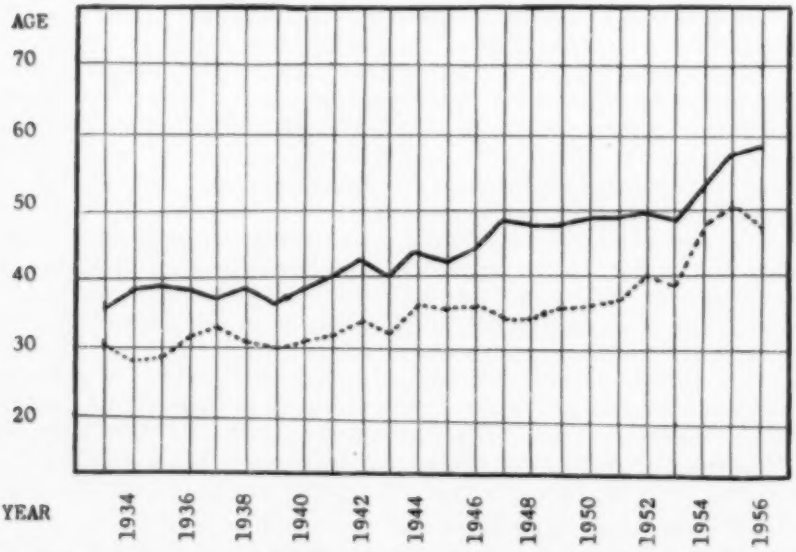

FIGURE 1: Average age of house patients at Worcester County Sanatorium, 1933 to 1956. The solid line represents men, the broken line women.

admissions for five years with an average of 700 admissions per year. The age of these patients ranged from 32 to 66. Seventeen had no previous evidence of tuberculosis, and in the other four the disease was considered inactive. The infection was usually of the acute pneumonic type and resulted in a mortality of 25 per cent. Boman[4] recently reported on 906 patients in four Swedish sanatoria. Forty-three had a history of peptic ulcer which preceded the onset of tuberculosis in 32 and followed the onset of tuberculosis in 11. In 20 cases tuberculosis occurred following gastrectomy, and in three it was found prior to operation. The author concludes that gastrectomy is a more important factor in the predisposition to tuberculosis than ulcers alone.

b. Peptic ulcer after treatment for pulmonary tuberculosis.

In this group we only point to a recent report of Callanan[5] who studied 27 cases of peptic ulcer among admissions for pulmonary tuberculosis at London Chest Hospital for a period of five years. Of the 23 who were subjected to some type of pulmonary surgery, 15 developed complications referable to ulcers, namely bleeding in eight and acute exacerbation of symptoms in seven. Webber and Gregg[6] observed 70 patients with benign gastric ulcer of whom 43 per cent were found to have chronic pulmonary disease, an incidence which was 3 times as high as in randomized patients.

The morbidity of peptic ulcers in this country has been estimated to range between 5 and 12 per cent. The mortality rate in 1953 was 5.6 per 100,000 population.[7] The death rate in men was six times as high as in women for gastric ulcer and seven times higher in duodenal ulcer. Advances in medicine and surgery have bettered the longevity of the victims of peptic ulcer as well as those of pulmonary tuberculosis. There has also been a steady increment in the incidence of tuberculosis in men of the older age group. In England, the incidence in men over 65 years of age has risen from 50 to over 80 per 100,000 population since 1938.[8] The average age of men at Worcester County Sanatorium has increased during the past 14 years from 40 to 58 (Fig. 1), a period of life which coincides with that of the highest incidence of peptic ulcer. One should also remember that peptic ulcer as well as pulmonary tuberculosis has been treated by surgical resection with mounting frequency.

It has been suggested that chronic pulmonary disease, and particularly emphysema, produces electrolyte changes which in turn may result in increased secretion of acid and pepsin in the stomach, but Polster[9] has demonstrated that this sequence of events occurs only in mild cases of tuberculosis while in advanced disease the gastric acidity decreases. Lucien[10] investigated the gastric chemistry of patients who had a history of dyspepsia or complained of it at the time of hospitalization. None of 250 patients showed normal values. One hundred sixty-three had elevated free and combined hydrochloric acid. Forty-eight had elevation of free hydrochloric acid and only 39 had hypochlorhydria. Lowell and associates[11] have emphasized the coincidence of smoking, emphysema and peptic ulcer.

The important factor of physical and emotional stress in the pathogenesis of peptic ulcer has been reiterated in the past several years and is the subject of an excellent discussion by Gray.[12] In this connection we are reminded that all 11 patients of our series who developed peptic ulcer following thoracic surgery or medical therapy had advanced pulmonary disease. The presence of physical and emotional strain was conspicuous in almost every case.

The theory which involves the irritating action of oral medication as a contributing factor in the development of peptic ulcer is well known. The effect of acetylsalicylic acid upon the gastric mucosa is a fitting example. Of the antituberculosis drugs para-amino-salicylic acid is most frequently responsible for gastrointestinal irritation in patients on oral chemotherapy and may justifiably be regarded as a contributing factor in the relapse of symptoms in chronic peptic ulcer. Perhaps of equal importance in the discovery of peptic ulcers is the search for the actual cause of symptoms which have been erroneously interpreted as the result of drug intolerance.

Another aspect of the problem is advanced by investigators who assume that electrolyte disturbances in the gastrectomized patient produce immunological changes resulting in the breakdown of the natural resistance of the lung parenchyma to the action of the tubercle bacillus. We rather favor the theory that the profound inadequacy of nutrition which usually complicates the status of the gastrectomized patient explains in itself a disposition to pulmonary tuberculosis and recurrences in individuals with a history of previous disease.

SUMMARY AND CONCLUSIONS

1. The coincidental occurrence of pulmonary tuberculosis and peptic ulcer has recently been observed with increasing frequency. Twenty-seven cases are here reported.

2. Tuberculous patients who develop gastrointestinal symptoms following thoracic surgery, oral chemotherapy, and especially PAS medication, should be investigated for peptic ulcer.

3. Patients who are subjected to gastrectomy for peptic ulcer should have preoperative chest x-ray films. If a pulmonary lesion is found, the presence of active tuberculosis should be ruled out. After the operation the lesion should be carefully followed in the immediate postoperative period as well as in the distant future.

4. Finally, a chest x-ray film should be part of the check-up examinations of all gastrectomized patients.

RESUMEN Y CONCLUSIONES

1. La coincidencia de tuberculosis pulmonar y úlcera péptica se ha observado con creciente frecuencia. Se han relatado 27 casos.

2. Deben investigarse en busca de úlcera péptica los enfermos que han sufrido cirugía torácica, o han tenido quimioterapia oral en especial con PAS.

3. Los sujetos a quienes se hace gastrectomía por úlcera péptica deben hacerse radiografía de tórax. Si se encuentra una lesión pulmonar debe investigarse si se trata de tuberculosis. Después de la operación la lesión debe ser cuidadosamente observada en postoperatorio inmediato y en el futuro distante.

4 Finalmente, una radiografía de tórax debe formar parte de rutina de revisión de todos los gastrectomizados.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

1. Das gleichzeitige Vorkommen von Lungentuberkulose und Peptischem Geschwür ist in letzter Zeit mit zunehmender Häufigkeit beobachtet worden. Hier wird über 27 Fälle berichtet.

2. Tuberkulöse Patienten, bei denen sich im Anschluss an thoraxchirurgische Eingriffe gastrointestinale Symptome entwickeln oder nach oraler Chemotheraphie und besonders PAS-Anwendung, sollten auf peptische Geschwüre untersucht werden.

3. Patienten, die wegen peptischem Geschwür einer Gastrektomie unterzogen werden, müssen vor der Operation eine Thorax-Röntgenaufnahme bekommen. Wird ein Lungenbefund erhoben, muss das Bestehen einer aktiven Tuberkulose ausgeschlossen werden. Nach der Operation muss der Befund sorgfältig überwacht werden, sowohl während der unmittelbaren postoperativen Periode als auch in fernerer Zukunft.

4. Schliesslich muss eine Thorax-Röntgenaufnahme zu einem Bestandteil der eingehenden Untersuchung aller gastrektomierten Patienten werden.

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The Symptom of Sighing: Physiologic and Pathologic Observations*

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A sigh is defined as a deep and prolonged audible inspiration and respiration of air, especially when involuntary and expressing some emotion or feeling: as grief, yearning, weariness or relief.[1]

Sighing is one of the characteristic patterns of most mammals, just as is eupnea, gasping and panting.[2] It is common in humans. Frequent sighing has for many years been considered a sign of nervous disturbance of respiration[3] and of neurocirculatory asthenia.[4] Sighing is apparently due to a spasm of the diaphragm.[5]

In the course of respiratory function studies in patients with various diseases of the lungs, heart and central nervous system sighing was observed not infrequently. These observations appeared to be of interest and will, therefore, be presented in this paper.

Material And Observations

In our observations we define a sigh as an involuntary respiratory peak that is 1.5 times or more the height of the tidal volume; this is slightly different from Caughey's definition,[6] according to which a sigh is twice as deep as the person's average breath.

I. Physiology of the Sigh

Four hundred and seventeen graphic records of the respiration (spirograms) of 330 individuals of the Medical and Tuberculosis Services of the Veterans Administration Hospital, East Orange, N. J., were examined for the presence of sighs. The spirograms were obtained by the routine method of determining the oxygen intake for basal metabolism studies and other pulmonary function data. The Collins nine liter respirometer with ventilograph pen was used for all measurements. Two six minute periods of quiet breathing of oxygen were examined for the presence of sighs. All volumes were corrected to B.T.P.S. (body temperature, ambient pressure, saturated with water vapor).

Of the 330 individuals, four were normals, about two thirds had various forms of pulmonary tuberculosis and the remainder had various cardiac and pulmonary diseases.

Of the 417 records, 93 were found to contain sighs. Of the 330 individuals, 81 (24.5 per cent) were represented in the group of records having sighs. Of the 81 individuals who sighed during quiet breathing 24 had repeat examinations. Eleven of the 24 had sighs in the repeat examinations. Of the 11, four had intervening thoracic surgery and one received

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cortisone for sarcoidosis. In these five cases, the results were treated as individual cases but were not used to change the patient count. In all other cases of duplicate records on the same individual, the results were averaged. This left a total of 86 records that had sighs.

Of the six women examined, four (66.7 per cent) had sighs in a total of six records. Of the 324 men, 77 (23.8 per cent) had sighs in a total of 87 records. Sighing was found in only one of the three normal women and the normal man.

Table I shows the distribution of the main diagnoses of the 81 individuals who showed sighing in their respiratory records.

The frequency of sighing in the 86 records was as follows: 48 (55.8 per cent) sighed once, 19 (22.0 per cent) sighed twice, seven (8.1 per cent) sighed three times, six (7.0 per cent) sighed four times, two (2.3 per cent) sighed 12 times, there was one record (1.2 per cent) each with five, 10 11 and 14 sighs.

The individuals ranged in age from 18 to 67 years. The average age was 38.3 years. Sixty per cent of the individuals were under 40 years old, 29 per cent between 40 and 60 and 10 per cent were over 60 years.

*A. The Sigh and the Vital Capacity**

The sigh volume ranged from 760 ml. to 3070 ml. with an average deflection from the base line of 1690 ml. Forty-four per cent of these sighs were under 1600 ml., 49 per cent were between 1600 and 2500 ml., 7 per cent were over 2500 ml. (Figure 1).

The observed vital capacity in these individuals ranged from 1360 ml. to 5850 ml., with an average of 3490 ml. This was on the average 87 per

TABLE I
DISTRIBUTION OF MAIN DIAGNOSIS IN 81 INDIVIDUALS WHO SIGHED

Normal	2
Tuberculosis, pulmonary	40
Tuberculosis plus emphysema	4
Tuberculosis plus bronchogenic carcinoma	1
Tuberculous pericarditis	1
Tuberculous pleurisy	6
Histoplasmosis	1
Coccidioidomycosis	1
Pneumoconiosis	1
Sarcoidosis	5
Hemoptysis, unknown origin	3
Asthma	2
Emphysema	3
Bronchiectasis	3
Bronchogenic carcinoma	1
Arteriosclerotic heart disease	3
Rheumatic heart disease	2
Cor pulmonale	2

*The terminology used in this paper is that of Pappenheimer, J. R., Chairman; Standardization of Definitions and Symbols in Respiratory Physiology, Fed. Proc., 9:602, 1950.

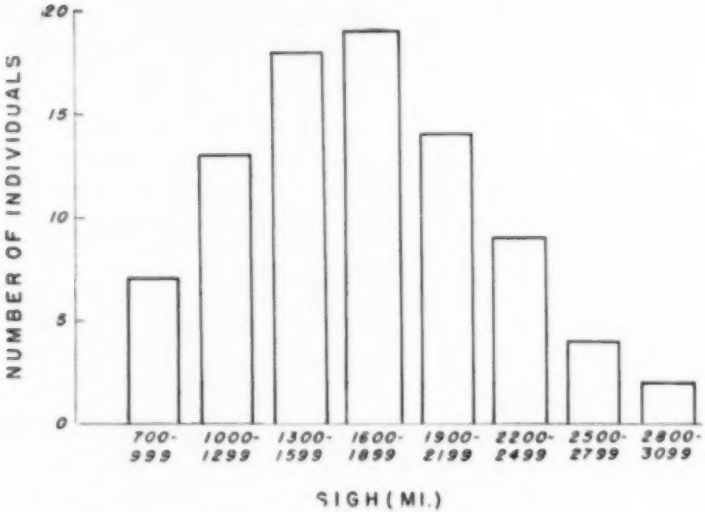

FIGURE 1: Distribution of sigh volume in 86 individuals.

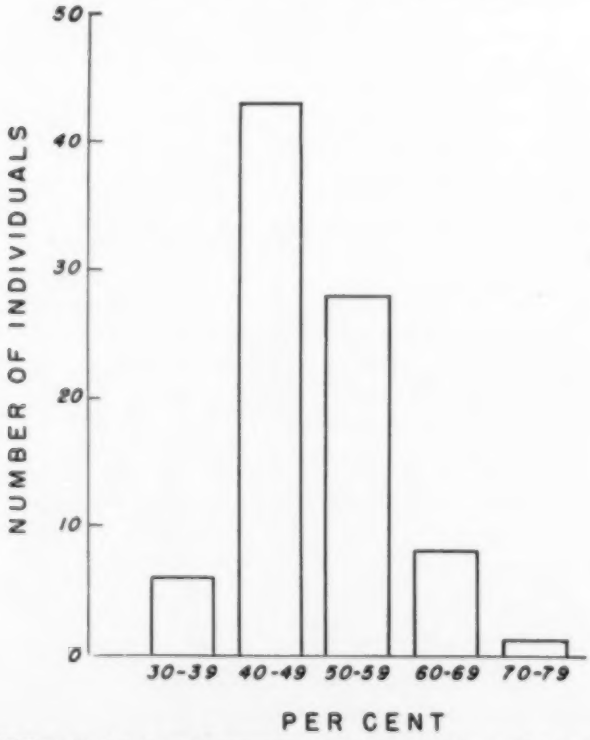

FIGURE 2: Sigh volume in percentage of vital capacity in 86 individuals.

cent of the predicted vital capacity. Predicted values for vital capacity were based on the regression formula of Baldwin and co-workers.[7] The range of the observed vital capacity/predicted vital capacity was from 39 per cent to 134 per cent. Twenty nine (33.7 per cent) of the individuals had vital capacities that were under 80 per cent of that predicted, 34 (39.6 per cent) were between 80 and 100 per cent and 23 (26.7 per cent) had vital capacities over 100 per cent of prediction.

The sigh ranged from 38 per cent to 70 per cent of the observed vital capacity wih a mean of 49.2 per cent (Figure 2) and a mean deviation of ± 5.8 per cent. The standard deviation was 7.3.

The linear regression of the vital capacity on the sigh was found to be: Vital capacity = 3488 ml. + 1.78 (ml. of sigh —1690 ml.). The coefficient of correlation, r, was found to be + 0.881. Figure 3 shows the scatter diagram with regression line of vital capacity on the sigh.

A reduced vital capacity had little effect on the average value for the percentage of the sigh of the observed vital capacity. Twenty nine indi-

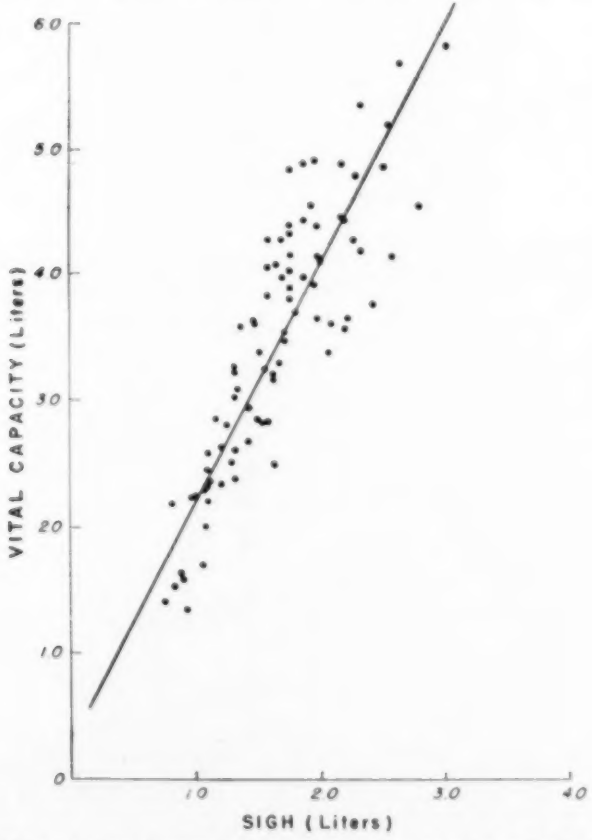

FIGURE 3: Scatter diagram with regression line of vital capacity on sigh.

viduals had vital capacities that were under 80 per cent of their predicted vital capacity. In these individuals, the average value of their observed vital capacity was 61 per cent of their predicted values and the relationship of the sigh to the observed vital capacity was 52.0 per cent. In the 34 individuals who had readings between 80 and 100 per cent of their predicted values the average per cent of observed vital capacity/predicted vital capacity was 91.3 per cent; the sigh was 48.7 per cent of their observed vital capacity. In 23 individuals the observed vital capacity was over 100 per cent of their predicted values. The average per cent of observed vital capacity/predicted vital capacity was 113.6 per cent. In these individuals the relationship, sigh/observed vital capacity, was 46.3 per cent.

B. The Sigh and the Subdivisions of the Vital Capacity

1. *Tidal volume*: The tidal volume ranged between 272 ml. and 1115 ml. with an average of 557 ml. Average values for tidal volume in healthy men under basal conditions are approximately 500 to 600 ml.

The mean deflection of the sigh was 310 per cent of the volume of the tidal volume. The range was between 160 and 620 per cent of the volume of the tidal volume. Three (3.5 per cent) were between 100 and 190 per cent of the deflection of the tidal volume, 37 (43.0 per cent) were between 200 and 290 per cent of the deflection of the tidal volume, 32 (37.2 per cent) were between 300 and 390 per cent of the deflection of the tidal volume, 14 (16.3 per cent) were 400 per cent or more the deflection of the tidal volume (Figure 4).

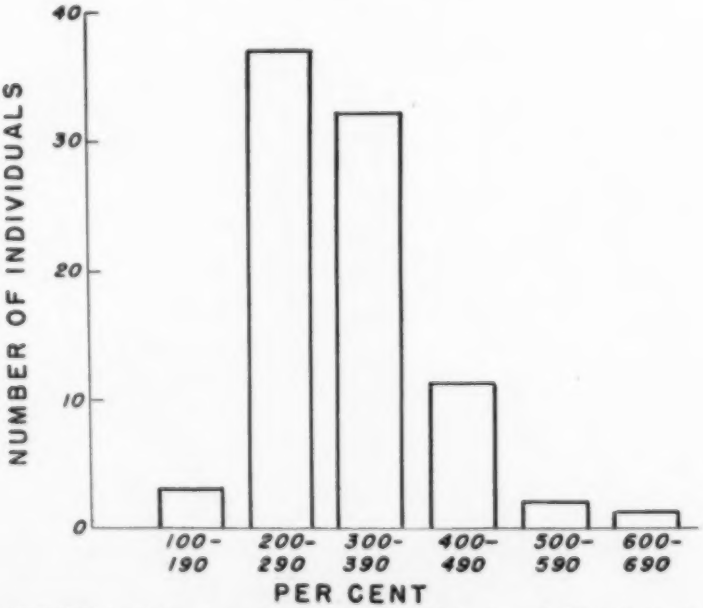

FIGURE 4: Sigh volume in percentage of tidal volume in 86 individuals.

In those cases where the sigh was from 100 to 190 per cent of the deflection of the tidal volume, the sigh was 50.7 per cent of the observed vital capacity. When the deflection was from 200 to 290 per cent the sigh was 47.9 per cent of the observed vital capacity. At 300 to 390 per cent, the sigh was 47.5 per cent of the observed vital capacity. At values of 400 per cent and higher, the sigh was equal to 55.7 per cent of the observed vital capacity.

2. *Inspiratory capacity*: The inspiratory capacity is the maximal amount of air that can be inhaled after normal expiration. It equals tidal volume plus inspiratory reserve volume.

The inspiratory capacity ranged from 1021 ml. to 4415 ml., with a mean of 2648 ml.

The sigh ranged from 44 per cent to 90 per cent of the inspiratory capacity with a mean of 65.1 per cent. The distribution is shown in Figure 5.

The linear regression of the inspiratory capacity on the sigh was found to be:

Inspiratory Capacity $=2648$ ml. $+ 1.34$ (ml. of sigh -1690 ml.) The coefficient of correlation, r, was found to be $+0.836$. Figure 6 shows the scatter diagram with regression line of inspiratory capacity on the sigh.

3. *Inspiratory reserve volume*: The inspiratory reserve volume is the maximal amount of air that can be inspired from the end-inspiratory position following a quiet inspiration; it is measured from the resting end-inspiratory level. It equals inspiratory capacity minus tidal volume.

The inspiratory reserve volume ranged from 690 ml. to 3763 ml., with a mean of 2080 ml.

The inspiratory reserve portion of the sigh was found to range from 33 per cent to 90 per cent of the inspiratory reserve volume itself, with a mean of 55.4 per cent (Figure 7).

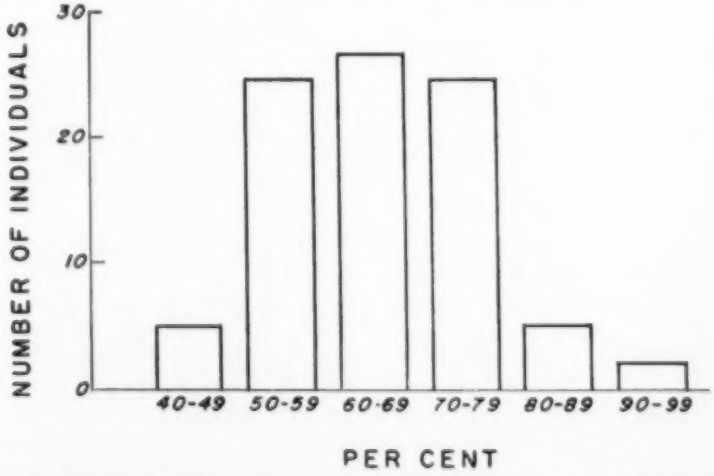

FIGURE 5: Sigh volume in percentage of inspiratory capacity in 86 individuals.

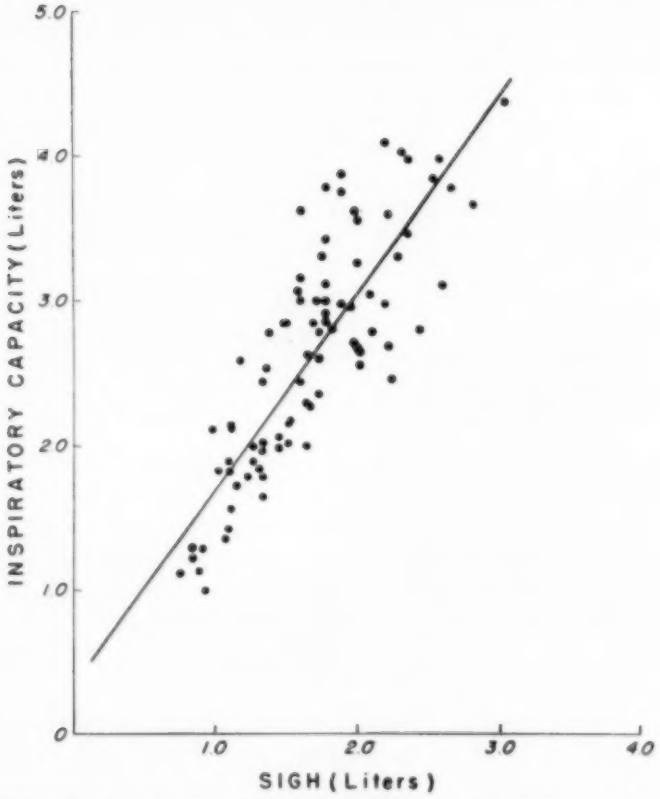

FIGURE 6: Scatter diagram with regression line of inspiratory capacity on sigh.

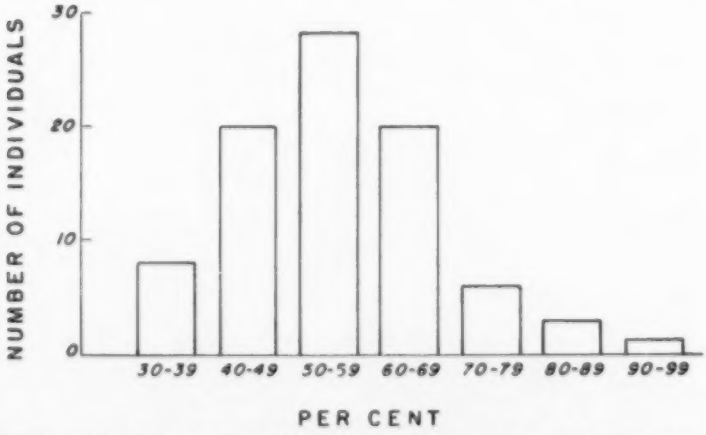

FIGURE 7: Sigh volume minus tidal volume in percentage of inspiratory reserve volume in 86 individuals.

C. The Sigh and Ventilation

1. *Tidal volume*: This has been discussed under the relationship of the sigh to subdivisions of the vital capacity.

2. *Frequency of respirations*: The number of respirations was six to 24 per minute, the mean being 13.8.

Of the 86 individuals who produced sighs, 11 (12.8 per cent) had respirations under 10 times per minute, 42 (48.8 per cent) from 10 to 14 times, 25 (29.1 per cent) between 15 and 19 times and eight (9.3 per cent) from 20 to 24 times per minute.

In all groups the sighing volume was of about the same percentage of the observed vital capacity (47.8 to 51.4 per cent).

3. *Ventilation equivalent*: Ventilation equivalent is defined as the amount of ventilation required for 100 ml. of oxygen uptake. Normally, this is from two to three liters. This is essentially a measure of efficiency of pulmonary circulation. The ventilation equivalent ranged from 1.7 to 4.9 liters, with a mean of 2.86 liters.

Sixty-three per cent had ventilation equivalents of 3.0 and lower, 37 per cent were 3.1 and higher. In the 54 individuals whose ventilation equivalent was 3.0 and lower the sigh was 48.8 per cent of the observed vital capacity and in the 32 individuals whose ventilation equivalent was 3.1 and higher the sigh was 49.8 per cent of the observed vital capacity.

D. The Sigh in Oxygen and Air Breathing

Another series of 340 records (mostly of patients with pulmonary tuberculosis) of breathing air for six minutes followed by a six minute period of oxygen breathing were examined for the presence of sighs. In 30 sighs occurred only when breathing air; in 17, only when breathing oxygen; and in 50 cases sighs were seen during air breathing and oxygen breathing. The occurrence of sighing is, therefore, not significantly diminished by oxygen; moreover, in a considerable number of cases it occurs on breathing oxygen only.

It has been shown,[8] that the number of sighs increases under re-breathing or carbon dioxide breathing, when sighing is normally present. If sighing is not normally present, it usually does not appear under these experimental conditions.

E. The Sigh in Bronchospirometric Recordings

The bronchospirometric recordings of 74 patients were examined for sighs. In six they were found in bronchospirometric as well as in the spirometric records.

Table II shows the relation of the sigh of the right lung to the total sigh. At an average it is 50 per cent. On the same table the vital capacity of the right lung in per cent of the total vital capacity is given; the average is 47 per cent. The relative sigh volume of one lung in relation to that of both lungs is parallel to the relative volume of the vital capacity of the respective lung.

TABLE II—THE SIGH IN BRONCHOSPIROMETRY

Patient	VC, Broncho-spirometry X 100 / VC, Spirometry	Right Lung	
		Vital Capacity Per Cent of Total	Sigh Per Cent of Total
1	90	29	37
2	96	37	45
3	88	34	32
4	97	47	50
5	91	78	76
6	84	55	60
Average	91	47	50

On bronchospirometry, the sigh (right + left) was found to be from 82 to 125 per cent of the sigh as found on spirometry, with a mean of 102 per cent. At the same time the vital capacity on bronchospirometry (right + left) was found to range from 84 to 97 per cent of the vital capacity as determined on spirometry, with a mean of 91 per cent.

II. The Sigh in Neurological Cases

Twenty graphic records of respiration of 11 patients of the Neurological Service were also examined for the presence of sighs. Fifteen records of eight patients showed sighing. Four records of two patients showed the type of sigh discussed above. Eleven records of six patients showed a different type of sigh. In these eleven records *the sigh was greater in volume than the voluntary vital capacity.* The reflex action involved in the sigh moved more air in and out of the lungs than the patient could do voluntarily. In all other patients the sigh volume was always smaller than the vital capacity.

The frequency of sighing in the records of the six neurological patients who showed sighs larger in volume than their vital capacity was as follows: Three sighed once and three twice. This lack of a greater frequency of sighing in the records of the neurological patients would appear to rule out a reflex adaptive mechanism to increase diminished respiration.

Of the two neurological patients who showed the typical sigh, one had a Guillain Barré syndrome and the other a basilar artery thrombosis. Of the six patients who showed sighs that were greater than their voluntary vital capacity, one had a brain injury of the right temporal area (gun shot); one had an ependymoma of the upper cervical cord; one had paralysis agitans; two had multiple sclerosis, and one had neurofibromatosis.

The following case histories give the pertinent data in four cases:

Case 1: R. J. D. This 32 year old white man, gave a history of having developed subcutaneous manifestations of neurofibromatosis between 1942 and 1945. In 1950 he began to have neurological symptoms in the left upper extremity, which became progressively more severe and extensive. Diagnosis of a cervical cord involvement was made following laminectomy in February, 1951. Since that time he has had three laminectomies. Extensive involvement of the cord at C-2 by tumor was noted. At present he has progressed to tetraplegia. The deep tendon reflexes have always been hyperactive.

The following is a record of his vital capacities and sighs:

	Vital Capacity	Involuntary Sigh
8-23-54	720 ml.	1050 ml.
9-15-54	900 ml.	1400 ml.
11- 9-54	930 ml.	1450 ml.
1- 2-55	810 ml.	1290 ml.
4-19-55	830 ml.	1190 ml.
6-13-56	560 ml.	1270 ml.

In each instance his involuntary sigh is larger than his voluntary vital capacity.

Case 2: R. R. This 30 year old white man, was in good health until July, 1953 when he experienced weakness and fatigue in his legs. He is now unable to walk, has difficulty in swallowing, his eyesight is impaired, he has loss of urinary control and no longer has spontaneous bowel movement. He has considerable muscular dystrophy and loss of deep tendon reflexes. His present diagnoses: (1) Multiple sclerosis, severe. (2) Paraplegia, spastic. (3) Paralysis of bladder, flaccid.

	Vital Capacity	Involuntary Sigh
August 26, 1954	700 ml.	1940 ml.

Graphs of the involuntary sigh and the voluntary vital capacity are shown in Figure 8.

Case 3: H. G. S. This 26 year old white man, sustained a penetrating wound of the right temporal area of the skull on March 17, 1953. Right temporal craniotomy was performed and the wound and missile tract debrided. Examination at time of respiratory studies showed; (1) Wound, penetrating, of right temporal region of brain. (2) Encephalomalacia of brain stem, upper part, due to trauma. (3) Quadriplegia, with hyperactive deep tendon reflexes.

	Vital Capacity	Involuntary Sigh
January 3, 1956	1410 ml.	3365 ml.

Case 4: M. J. This 73 year old white woman, was in good health until 1949, when she experienced pain at the back of her neck. The pain continued and became progressively more severe. Early in 1952, she began to experience weakness in the extremities on the right side. She entered the hospital and a diagnosis of a cord tumor was made. An operation for removal of the tumor from the cervical cord was performed in April, 1952. She now has a quadriplegia and is confined to bed. Her diagnosis is (1) Ependymoma, upper cervical cord, post operative status. (2) Quadriplegia, with hyperactive deep tendon reflexes.

	Vital Capacity	Involuntary Sigh
April 13, 1956	380 ml.	715 ml.

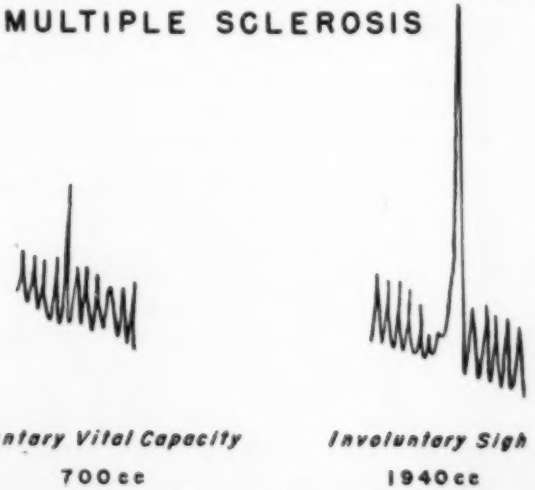

FIGURE 8: Voluntary vital capacity and involuntary sigh in patient with multiple sclerosis.

Discussion

Sighing, which is a deep inspiration, is usually described as a sign of neurocirculatory asthenia[3, 4] and is common in neurotics.[9] However, it occurs in many healthy as well as sick individuals. Sighing respiration was seen in the spirograms of 81 of 330 individuals who, when undergoing pulmonary function tests, were breathing oxygen for two 6-minute periods. Among these were healthy people and patients with various forms of pulmonary and cardiac diseases, in all age groups.

When the volume of the sigh is compared with the vital capacity in the same subject, a direct correlation can be found between these two measurements: A larger vital capacity permits a larger sigh, a diminished vital capacity causes diminution of the sigh. A similar correlation exists between inspiratory capacity and sigh. The tidal volume, however, does not affect the size of the sigh: In our observations the sighs ranged from 160 to 620 per cent of the tidal volume. Neither did the rate of respiration or ventilation equivalent show any relation to the size of the sigh.

Sighing respiration may occur while breathing air as well as while breathing oxygen. Most of our patients whose spirograms were recorded with air and oxygen inhalation produced sighs under either condition. In a minority, sighing was observed when either breathing air or when breathing oxygen.

Bronchospirometric examinations, in spite of local anesthesia, excitement, trauma, stenosis breathing, does not abolish the sighing respiration.

The volume of the sigh is, as expected, usually smaller than the vital capacity of the same individual, However, to our greatest surprise, we observed the opposite in six patients with various neurological involvements. In these patients the involuntary sigh was greater—sometimes considerably greater, than the vital capacity. These patients had as different diseases as: Brain injury of the right temporal area; ependymoma of the upper cervical cord; paralysis agitans; multiple sclerosis; neurofibromatosis. All these patients had low vital capacities.

Sighing is considered to be a reflex, and the intensity of this reflex was apparently increased in this group of patients. However, the lack of a greater frequency of sighing in the records of the neurological patients would appear to rule out a reflex adaptive mechanism to increase diminished respiration. If we compare it with the deep tendon reflexes, there did not seem to be a correlation: Although four of these six patients had hyperactive deep tendon reflexes, normal reflexes were found in one and loss of deep tendon reflexes was found in one.

Sighing disappears during sleep and therefore, is believed to be of cortical origin.[10] It is sensitive to voluntary control and to the emotions.[11] Induced unpleasant ideas increase the number of sighs.[9] However, in experiments in dogs sighing respiration was demonstrated in medullary preparations. "The rhythm of the sighing type of breathing is more pronounced in midcollicular and pontine preparations and is enhanced by vagotomy. At all levels, but particularly at the midcollicular and pontine

levels, there is pronounced inhibition of eupnea by the sighing respiration. This occurs after vagotomy and is thus not dependent upon pulmonary reflexes initiated by the deep breath."[12]

Sighing respiration can be produced in dogs by morphine.[13] None of our patients had received morphine prior to the recording of their respiration and morphine plays no role in our observations.

Whalen[2] states: "Since sighing has been revealed in experimental animals only after transection of the brain stem and vagotomy, or after severe hypoxia in intact animals, the cause of the sighing seen in the present experiments is an enigma." Similarly we may say from our own observations: The cause of the large volume of the sigh in our six neurological patients as compared with their voluntary vital capacity is an enigma.

SUMMARY

A sigh is defined as a deep inspiration, 1.5 times or more of the tidal volume.

In 417 spirograms of 330 individuals (normals and patients with various pulmonary and cardiac diseases) taken during two six minute periods of oxygen breathing, 93 spirograms of 81 individuals showed sighs.

Patients with larger vital capacities produced larger sighs than those with smaller vital capacities. A similar parallelism existed between inspiratory capacity and sigh volume. No correlation was found between tidal volume and sigh volume.

In another series of studies it was seen that sighs occur under air breathing as well as under oxygen breathing.

Sighing respiration could also be recorded during bronchospirometric studies.

Six patients with various neurological disorders produced sighs greater in volume than their vital capacities. The sigh is apparently caused by a reflex which was not disturbed in these patients in whom the pathway for a voluntary deep breath had been damaged.

RESUMEN

Se define un suspiro como una inspiración profunda, 1.5 veces o más que el aire corriente.

En 417 espirogramas de 330 individuos (normales y enfermos de varias afecciones pulmonares y cardiacas) tomados durante dos períodos de seis minutos de respirar oxígeno, se encontraron 93 suspiros de 81 individuos.

Los enfermos con mayor capacidad vital produjeron más amplios suspiros que aquéllos con pequeñas capacidades vitales. Existe un paralelismo semejante entre la capacidad inspiratoria y el volumen del suspiro. No se encontró correlación entre el aire corriente y el volumen del suspiro.

En otra serie de estudios se ha visto que el suspiro ocurre al respirar aire lo mismo que al respirar oxígeno.

La respiración susporisa puede también observarse durante los estudios broncoespirométricos.

En seis enfermos con varios trastornos neurológicos se produjeron suspiros mayores en volumen que sus capacidades vitales.

El suspiro es causado aparentemente por un reflejo que no tué perturbado en aquellos enfermos en quienes la vía para producir una respiración profunda voluntaria ha sido danado.

ZUSAMMENFASSUNG

Ein Seufzer wird definiert als eine tiefe Inspiration, 1,5 mal oder mehr des Atemvolumens umfassend. Von 417 Spirogrammen von 330 Personen (Gesunde und Kranke mit verschiedenen Lungen- und Herzkrankheiten) aufgenommen während 2 Sechsminuten-Perioden unter Sauerstoffatmung, zeigten 93 Spirogramme von 81 Personen Seufzer.

Patienten mit höherer Vitalkapazität hatten stärkere Seufzer als solche mit geringerer Vitalkapazität. Eine ähnliche Paralelle bestand zwischen Einatmungsluft und Seufzervolumen. Eine Korrelation wurde nicht gefunden zwischen Atemvolumen und Seufzervolumen.

Einer anderen Untersuchungsreihe war zu entnehmen, dass Seufzer vorkommen sowohl bei Luftatmung wie bei Sauerstoffatmung.

Seufzeratmung konnte ferner im Verlauf von Bronchospirometrischen Untersuchungen aufgenommen werden.

6 Patienten mit verschiedenartigen neurologischen-Störungen hatten Seufzer, deren Volumina grösser waren als ihre Vitalkapazität. Der Seufzer entsteht wahrscheinlich durch einen Reflex, der nicht unterbrochen ist bei solchen Patienten, bei denen die Leitung für eine willkürliche vertiefte Atmung gestört ist.

Acknowledgment: The writers gratefully acknowledge the cooperation of Dr. W. O. Howard, Chief, Neurology Section; and the Medical Illustration Department of the Veterans Administration Hospital, East Orange, New Jersey.

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SECTION ON CARDIOVASCULAR DISEASES

Proximal Interruption of a Pulmonary Arch (Absence of One Pulmonary Artery): Case Report and a New Embryologic Interpretation

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Congenital absence of the right or left pulmonary artery is a rare anomaly, with less than 50 cases in the medical literature. Although Frantzel[1] is generally credited with having described the first case of this type, his case was atypical, since it involved an "aortic-pulmonic" defect and had a right pulmonary artery arising from the ascending aorta. This pulmonary artery was probably an "ectopic" pulmonary artery, resulting from abnormal aortic-pulmonic septum formation, and not an "absent pulmonary artery" in the usual sense. The first typical autopsied case to be reported was that by Döring.[2] Subsequent cases have been diagnosed at autopsy[3-6] and at operation.[7, 8] Madoff, et al,[9] in their review of the subject in 1952, were the first to report the successful clinical diagnosis of this condition, utilizing angiocardiography. Since then, numerous authors[10-19] have reported cases similarly diagnosed. Cardiorespiratory data were included in some of these case reports.[9, 11, 13] To the best of our knowledge, no published case has had proved pulmonary hypertension. The following case report is therefore unique in this regard.

Case Report

B. P. (U. H. 887346), a male infant, was born on February 11, 1955, following an uncomplicated, full term pregnancy. Delivery was spontaneous and normal. The birth weight was 4225 grams. There was no neonatal complication, although from birth he was noted to have deep but not labored respirations. At the age of seven weeks he had the first bout of "pneumonia," characterized by low grade fever and rapid respirations. He was treated at home with intramuscular penicillin, with apparent recovery in a few days. During subsequent months the infant had two similar episodes and was again treated at home.

Between the ages of four and six months, he had two rather severe bouts of pneumonia, both of which required hospitalization. Cardiomegaly was first noted at the age of five months, together with circumoral cyanosis on exertion and crying. Because of the repeated bouts of pneumonia and enlarging heart size, he was referred to University Hospitals on August 10, 1955, for further evaluation. Growth and development up to this time had been normal.

From the Department of Pediatrics, University of Minnesota. Dr. Char was a Trainee in Cardiology, National Heart Institute, United States Public Health Service. This study was aided by a grant from the Minnesota Heart Association.

On physical examination the infant was noted to have slight tachypnea and mild circumoral cyanosis. His weight was 7800 grams and his length was 70 centimeters. A few moist rales were heard in both lungs. The heart was enlarged to percussion. A grade 1 systolic murmur was heard best in the fourth and fifth left intercostal spaces along the left sternal border and the pulmonic second sound was noted to be slightly accentuated. The liver was palpable just below the right costal margin. The electrocardiogram showed right axis deviation, right ventricular preponderance greater than normal for age, and abnormally peaked P waves. Roentgenographic studies showed a moderately enlarged heart with prominence of the pulmonary artery segment and the right ventricle. The pulmonary vascular markings in the left lung appeared increased but those in the right lung appeared decreased (Figure 1). An angiocardiogram showed absence of filling of the right pulmonary artery (Figure 2). He responded well to digitalization and was therefore discharged on September 11, 1955.

He was readmitted three weeks later because of dyspnea, circumoral cyanosis, and pulmonary congestion. He improved with antibiotic therapy. Because of the known occurrence of associated cardiac malformations in patients with absence of a pulmonary artery, cardiac catheterization was done on October 10, 1955. The findings suggested a patent ductus arteriosus (Table I), so a retrograde aortogram was done the following day in an attempt to better identify such a defect. This study demonstrated multiple fine collateral vessels arising from the aorta and passing to the right chest, as well as a larger vessel arising from the left subclavian artery and crossing over to the right chest (Figure 3). No patent ductus arteriosus was demonstrated.

The patient was discharged from the hospital on October 24, 1955, but subsequently required repeated hospitalizations because of severe dyspnea and cyanosis. He failed to gain weight and his cardiac status gradually worsened. Auricular fibrillation and flutter developed. A repeat angiocardiogram was performed in the antero-posterior view, to check for a possible localized obstruction of the right pulmonary artery. Again, there appeared to be complete absence of the right pulmonary artery (Figure 4). Because his condition was deteriorating rapidly, a repeat cardiac catheterization was done

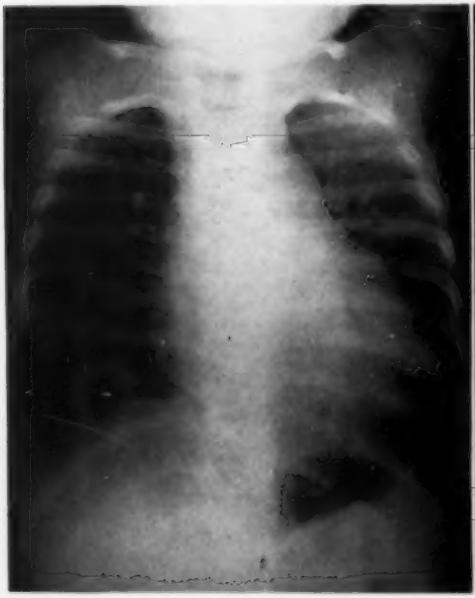

FIGURE 1

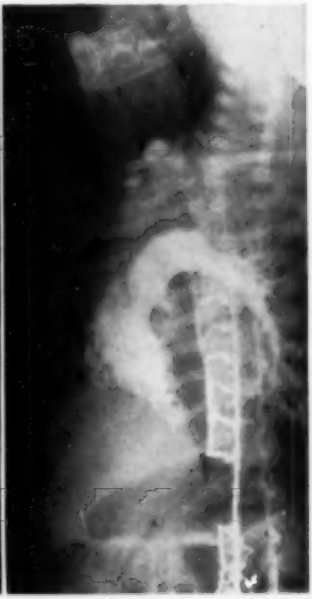

FIGURE 2

Figure 1: Roentgenogram of the chest (antero-posterior view), demonstrating cardiomegaly, prominent main pulmonary artery segment, and decreased pulmonary vasculature on the right side.—*Figure 2:* Angiocardiogram (right posterior oblique view), demonstrating absence of the right pulmonary artery.

TABLE I

CARDIAC CATHETERIZATION DATA

	Age 8 Months—Oct. 10, 1955			Age 13 Months—March 9, 1956		
	Pressure In Mm. Hg.	Oxygen Content In Volumes/100 cc. (Van Slyke)	Per Cent Oxygen Saturation	Pressure In Mm. Hg.	Oxygen Content In Volumes/100 cc. (Van Slyke)	Per Cent Oxygen Saturation
Pulmonary artery	56/20 Mean 33	9.14	56.63	110/80 Mean 90	5.40	40.54
Right ventricle	56/0	7.27	45.04	110/0	5.46	40.99
Right atrium		8.03	49.75		5.93	44.52
Inferior vena cava		7.99	49.50		4.59	34.59
Superior vena cava		7.40	45.85		4.74	35.59
Femoral artery		15.56	94.55		11.02	80.48

Total Pulmonary Resistance: Oct. 10, 1955—2585 dynes sec. $cm.^{-5}$
March 9, 1956—6200 dynes sec. $cm.^{-5}$

on March 9, 1956, in the hope of revealing a correctable intracardiac defect. This study showed a further marked increase in pulmonary artery pressure but no left to right shunt (Table I).

He was admitted to the hospital for the last time on April 4, 1956, with marked cardiomegaly and severe congestive failure. He died two days later.

Autopsy findings: There was complete symphysis pleurae on the right side. The heart was markedly enlarged, particularly the right ventricle. The valves and endocardium were normal. The ventricular septum was intact and the foramen ovale was closed. The great vessels arose in the usual manner but the main pulmonary artery gave rise only to an enlarged left pulmonary artery (Figure 5). The coronary vessels and pulmonary veins were normal. A ductus arteriosus, measuring 1.5 millimeters in diameter, connected with the left pulmonary artery but not patent. An obliterated vessel, measuring 1.5 millimeters in diameter (probably a right ductus arteriosus) arose from the proximal portion of the innominate artery and passed to the hilum of the right lung. At the hilum this vessel joined a widely patent vessel 4 millimeters in diameter which then branched to supply the various lobes of the lung. The branch of the left subclavian artery demonstrated by aortography was not identified, and apparently supplied the surface of the lung rather than the hilum. The left lung was firm and had lost its crepitance. On cut section, this lung exuded large amounts of bloody froth. The right lung was smaller than the left and had several areas of congestion and atelectasis. Sections of both lungs were examined microscopically by Dr. Donald F. Ferguson of the Veterans Administration Hospital, Minneapolis, Minnesota. A Verhoeff-Van Gieson elastic stain was used. The left lung showed severe

medial hypertrophy of the small arteries but no intimal proliferation was noted in any vessels less than 150 microns in diameter. The veins and capillaries appeared normal (Figure 6). Sections from the right lung were strikingly different. The pulmonary arteries in this lung had very thick and dense adventitia, and seemed rather small in comparison to the adjacent bronchi. The smaller arterioles, so prominent in the left lung, were hardly distinguishable. There was no evidence of medial or intimal lesions in the pulmonary arterial vessels in the right lung (Figure 7). The veins and capillaries were normal.

Discussion

Embryologic Features

Among published cases of absent left or right pulmonary artery there is a preponderance of the former. The former tends to be associated with an intracardiac defect, particularly tetralogy of Fallot, while absence of the right pulmonary artery generally occurs as an isolated finding.[18, 20] There have been at least five cases of absent right pulmonary artery described with an associated patent ductus arteriosus,[1, 2, 4, 11, 19] and in two of these there was also a coarctation of the aorta.

McKim and Wiglesworth[15] reviewed the embryologic aspects of this defect in considerable detail, and emphasized that the aortic arch is usually on the side opposite to the absent pulmonary artery. Thus, absent left

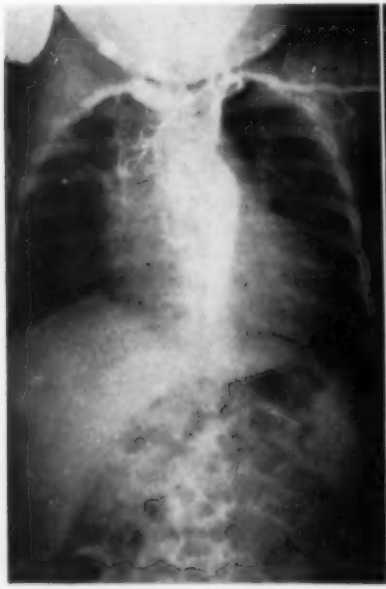

FIGURE 3

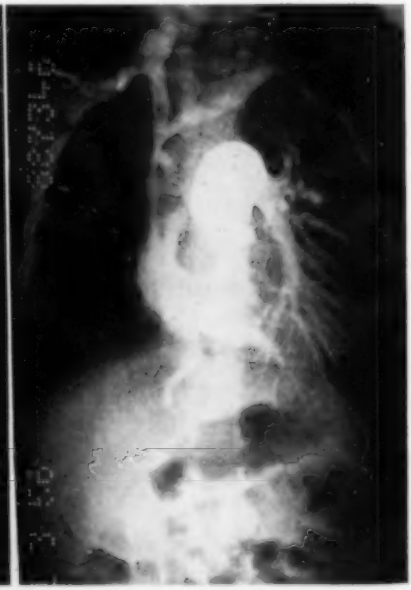

FIGURE 4

Figure 3: Retrograde aortogram (antero-posterior view), demonstrating bronchial arteries and an anomalous branch from the left subclavian artery passing to the right chest.—*Figure 4:* Angiocardiogram (antero-posterior view), demonstrating absence of the right pulmonary artery.

pulmonary artery often occurs in tetralogy of Fallot having a right aortic arch. These authors described an anomalous vessel running from the innominate artery to the left lung hilum in three cases with right aortic arches and interpreted this vessel as an obliterated left ductus arteriosus. They considered that the heart end (the ventral portion of the sixth arch) of the left pulmonary artery had disappeared, while the ductus arteriosus (the dorsal portion of the sixth arch) had remained in continuity with the distal portion of the left pulmonary artery, first as a functioning vessel and later as a fibrotic non-patent structure. McKim and Wiglesworth also suggested that the aortic bud (dorsal portion of the sixth arch) may have grown directly into the pulmonary plexus without there having been a pulmonary artery *per se*, but considered this a less likely possibility in view of the normal anatomical development of the hilar and intrapulmonary arteries in these cases.

Emanuel and Pattinson[20] called attention to the presence of developmental defects of the bulbis cordis (as in tetralogy of Fallot) in cases

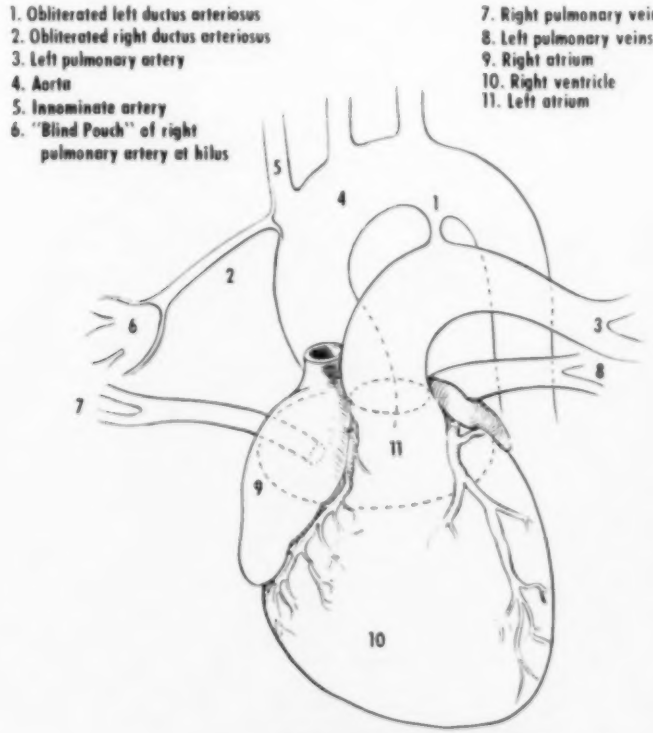

FIGURE 5: Drawing of autopsy specimen, showing connection of right ductus arteriosus (obliterated lumen) to right pulmonary artery.

where a left pulmonary artery is absent, and attributed the latter to faulty absorption of the left sixth arch. They stated that if the conventional view of symmetrical development of the two pulmonary arteries is accepted, the foregoing association could not be explained. They pointed out that this still did not explain the association of absent right pulmonary artery with normal intracardiac anatomy, though they suggested that in such cases perhaps the proximal portion of the right sixth arch became involved in the normal absorption of the left sixth arch.

To us, the observations and interpretations of both the foregoing groups, as well as those of the embryologists, Bremer[21] and Congdon,[22] can best be brought together as follows. The aortic (fourth) arches begin symmetrically, but unilateral dominance develops rapidly. Similarly, the sixth arches begin symmetrically, but deviate at about the time that the arterial trunk is becoming divided (Figure 8a). The dorsal or ductal portion (B) of the pulmonary arch on the side opposite to the dominant pulmonary arch (carrying the greater blood flow) normally undergoes degeneration. This allows a straightening out of the pulmonary artery on this side, and also combines with the action of the increasing blood current to permit the pulmonary trunk and other pulmonary arch to align. The result in the normal individual is that the main pulmonary artery is derived from the pulmonary trunk and some of the proximal portion (A) of the left pulmonary arch; the left pulmonary artery consists of

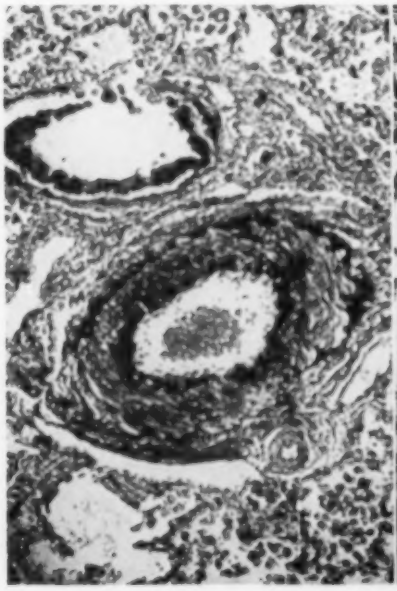

FIGURE 6

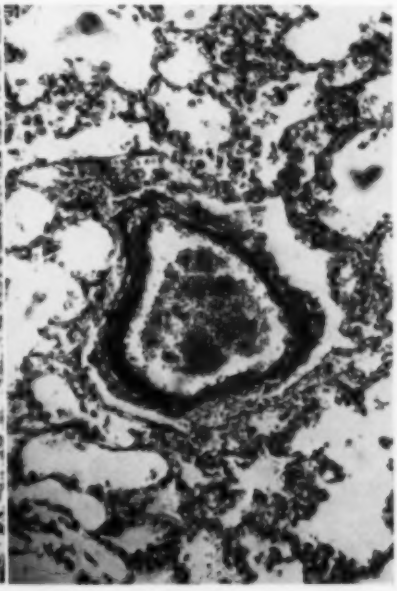

FIGURE 7

Figure 6: Photomicrograph of small artery from left lung, demonstrating marked medial hypertrophy.—*Figure 7:* Photomicrograph of small artery from right lung, demonstrating normal arteriolar wall and thick adventitia.

the primitive left pulmonary artery; and the right pulmonary artery consists of the primitive right pulmonary artery plus a portion (D) of the right pulmonary arch (Figure 8c). Thus there is definite asymmetrical

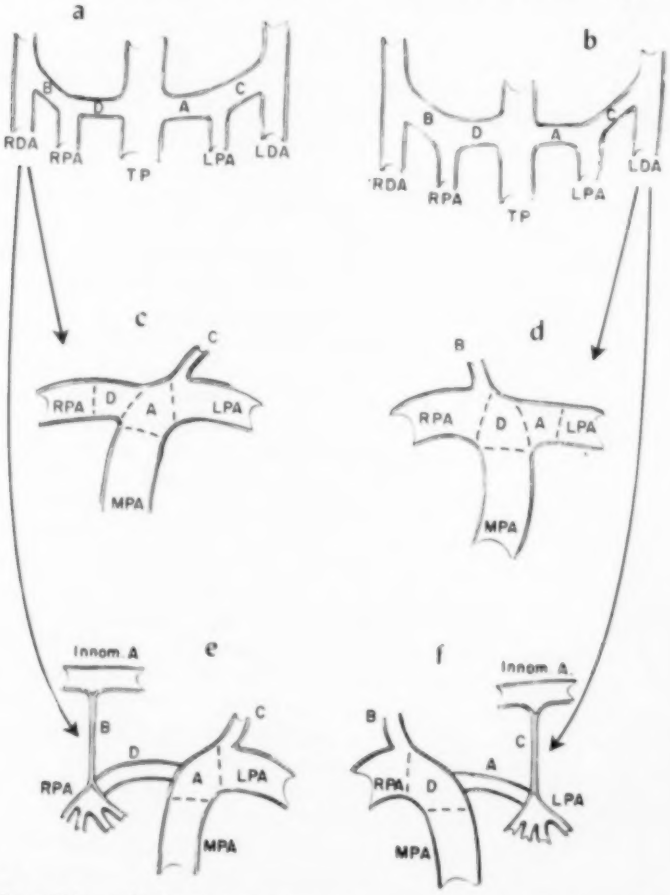

FIGURE 8: a. Schematic diagram of pulmonary arch system at early stage of normal development. The terminology of Emanuel and Pattinson[20] has been followed for ease of comparison. Proximal (ventral) portion of pulmonary arch designated as "A" on left and "D" on right, and distal (dorsal or ductal) portion designated as "C" on left and "B" on right. Left and right primitive pulmonary arteries designated as "LPA" and "RPA." Pulmonary trunk indicated by "TP," and left and right descending aortae, by "LDA" and "RDA." b. Comparable diagram in case where the right pulmonary arch becomes dominant. c. Standard adult pattern of pulmonary vessels, with embryologic derivatives indicated. "MPA" indicates main pulmonary artery. d. Comparable adult pattern where right pulmonary arch was dominant. e. Adult pattern in case of absent right pulmonary artery. The left ductus arteriosus (shown as being patent here) indicated by "C," the right ductus arteriosus (shown as being obliterated) indicated by "B," and the underlying arch defect (interruption) indicated by "D." f. Adult pattern in case of absent left pulmonary artery. The right ductus arteriosus (shown here as being patent) indicated by "B," the left ductus arteriosus (shown here as being obliterated) indicated by "C," and the underlying arch defect (interruption) indicated by "A."

development of the definitive pulmonary arteries. The direction of asymmetry is probably dependent primarily on the characteristics of the aortic sac and anterior arches, the fourth in particular (which determines the location of the definitive aortic arch). Blood flow is certainly involved in this deviation in symmetry, but it is difficult to distinguish cause from effect in this regard. It is well to remember that the normal interruption of the right pulmonary arch (ductal portion or B) takes place prior to the normal interruption of the right fourth arch.

One can theorize that if the dorsal portion (B) of the pulmonary arch on the side opposite the definitive aortic arch persists (perhaps due to blood flow factors), there will be interference with the development described above, and the ventral portion (D) of this pulmonary arch may then be obliterated. This will result in an "absent pulmonary artery" on this side, or rather in "proximal interruption of the pulmonary arch" (Figure 8e). The primitive pulmonary artery will remain intact, but will connect with the dorsal (B) portion (which will usually be subsequently recognized only as a fibrotic structure best identified as a ductus arteriosus, but which may persist as a patent vessel) rather than with the ventral portion (D) of the pulmonary arch (which would normally be incorporated into the definitive pulmonary artery). The absent pulmonary artery will always occur on the side opposite the larger ductal (dorsal) arch segment. Since the normal heart usually has a left aortic arch and a left ductus arteriosus, the absent pulmonary artery will usually be on the right side. In abnormal hearts with right aortic arches, the larger ductal segment would generally be expected to be on the right side (Figure 8b), and an absent pulmonary artery would then be on the left side (Figure 8f). In cases of absent left pulmonary artery with defects of the bulbis cordis, but with left aortic arches, one must assume that the dominant pulmonary arch was on the right. Likewise, for those very rare cases of normal heart with left aortic arch and absent left pulmonary artery, one must assume that the dominant pulmonary arch was on the right. The development of large bronchial vessels from the aorta to the affected lung in these cases can be viewed as a secondary process.

Our theory appears to explain all cases. It differs greatly from that of Emanuel and Pattinson[20] in that these workers implicated faulty absorption of the segment on the side of the ductus (dominant ductal side), whereas we implicate degeneration of the corresponding segment on the opposite side. It differs from the interpretation of McKim and Wiglesworth[15] in that the latter workers did not refer to possible reversal of the dominant pulmonary arch in their cases of absent left pulmonary artery, and did not stress the asymmetrical development of the pulmonary arteries. Since we ascribe great significance to the location of the dominant pulmonary arch (and its ductal segment), the next question which arises has to do with the factors determining arch dominance. We have already assumed that the development features of the fourth arches will influence those of the sixth arches. In addition, one can assume that faulty differentiation of the aortic sac and arterial trunk (common trunk) will

affect the location of the dominant pulmonary arch through its effect on the fourth arches, but may also be of more direct influence at times (as in tetralogy of Fallot with left aortic arch but with absent left pulmonary artery, and therefore a dominant right pulmonary arch by our theory). Actually, the bulbis cordis defects may well be a result of faulty aortic sac and arterial trunk differentiation, and the association of bulbis cordis defects with absent pulmonary artery probably is not one of cause and effect.

The association noted between absent right pulmonary artery and abnormalities of the great vessels does not conflict with this theory, but is just as one might expect if arch differentiation is abnormal. The infrequent occurrence of bilateral ductus arteriosus in cases of otherwise normal hearts and pulmonary arteries is certainly in line with our theory, yet its rare occurrence in no way negates it. Moreover, it fits those cases of truncus arteriosus having absence of one pulmonary artery. If the left pulmonary artery is absent in such cases, the right pulmonary artery arises from the right posterior aspect of the truncus; if the right pulmonary artery is absent, the left pulmonary artery arises from the left posterior aspect. Collett and Edwards[23] list one case (Dickson and Fraser[24]) which would appear to be an exception, inasmuch as the right pulmonary artery was listed as arising from the left side of the truncus; however, examination of the original paper shows the description and drawing to be indeterminate and confusing on this point. Another case (Shapiro[25]) of truncus is pertinent to the earlier discussion; this case had a left pulmonary artery arising from the left side of the trunk and a right innominate artery giving off a branch to the right lung; this latter vessel was not referred to as a ductus arteriosus, but it is certainly very suggestive of such a structure in view of the embryologic features already described.

Diligent search for residual ductal structures in specimens of truncus arteriosus lacking both pulmonary arteries (given a separate classification by most workers) may demonstrate such structures. This would of course immediately identify them as close relatives of cases with pulmonary arteries, since the presence of a ductus arteriosus indicates the earlier presence of a pulmonary arch. It is much easier to accept faulty differentiation of the pulmonary arches, with subsequent degeneration of various structures, than to visualize complete failure of the sixth arches to form. Failure of clear-cut dominance of one or the other pulmonary arch may result in two pulmonary arteries each with a functioning ductus arteriosus or in bilateral interruption of the proximal portions of the pulmonary arches. Although this suggestion is included largely for speculation, the observation that unilateral absence of a pulmonary artery is apparently not due to an absence of a pulmonary arch should make one hesitant in invoking such an explanation for absence of both pulmonary arteries. There may well be similar or closely related factors involved in the development of all defects of the aortic and pulmonary arches, truncus, and bulbis cordis.

Since in all cases of absent pulmonary artery there appears to be

simply a break in pulmonary arch continuity, it would appear more appropriate to term this defect as "proximal interruption of the pulmonary arch." The primitive pulmonary arteries *per se* remain intact, whereas the proximal arch component of the definitive pulmonary artery is deficient. Normally there is "distal interruption" of the pulmonary arch, so one must be careful to refer to these cases as "proximal interruption." Interruption of the pulmonary arches has much in common with interruption of the aortic arches, since in the latter too there is normal as well as abnormal interruption. Likewise in each there may be failure of interruption, giving bilateral ductus arteriosus in the former and double aortic arch in the latter.

The functioning of the ductus arteriosus before birth probably accounts for the failure of large bronchial arteries to develop on the involved side. Also, it probably allows a near-normal development of the lung on the affected side.[15] The decreased size of the lung on the affected side, as described in the majority of published cases, may well be due to differential postnatal growth resulting from differences in blood supply.[15]

The autopsy findings in our cases followed exactly the pattern described by McKim and Wiglesworth,[15] and like two of their cases, involved bilateral ductus arteriosus. Our case, like that of Emanuel and Pattinson[20], showed highly vascular adhesions between the affected lung and the chest wall. (We assume that the branch from the left subclavian artery demonstrated by aortography supplied blood to this area.)

Clinical and Physiological Features

If present as an isolated defect, congenital absence of one branch of the pulmonary artery has been usually described as essentially asymptomatic. However, there may be a slight decrease in exercise tolerance and pneumonitis is said to be fairly common in the involved lung. Hemoptysis occasionally occurs, and in at least one case rupture of an arteriosclerotic bronchial vessel was established as the cause of death.[13]

Absence of one of the pulmonary arteries can often be diagnosed on the ordinary chest roentgenogram[12, 17]. The involved hemithorax is smaller and the heart and mediastinum are shifted to that side. The involved lung is very radiolucent. As mentioned earlier, angiocardiography provides an exact diagnosis. Cardiac catheterization has been performed in only a few of the reported cases[9, 11, 13], and in these the resting pulmonary artery pressures were normal, with only a slight increase on exercise. In the present case, aortography was useful in demonstrating the collateral blood supply to the affected chest, and in retrospect, indicated that the ductus arteriosus on each side was not patent.

Studies of pulmonary function in published cases showed either normal or slight reduction in vital capacity, residual volume, and total lung volume[9, 11]. Bronchospirometric studies using room air demonstrated normal ventilation in the involved lung but non-participation in oxygen uptake.[9, 11, 18] It has been shown experimentally that as much as one third of the output of the left ventricle may go to the bronchial arteries of a lung in which the pulmonary artery has been ligated.[26] Findlay and Maier[7]

suggested that the patient with a congenitally absent pulmonary artery may be benefited by the removal of the lung on the affected side, thereby decreasing the load on the left ventricle.

The pulmonary pathology found in our patient was unsual. The medial hypertrophy in the small arteries of the left lung was severe, the average cross-section area of the lumen being only about 12% of the total average cross-section area of the artery. This degree of narrowing was probably sufficient to account for the high calculated total pulmonary resistance obtained at each cardiac catheterization. The left lung of this patient accepted the total right ventricular output, and pulmonary flow in this lung could therefore be assumed to be twice normal. These pulmonary changes differed somewhat from those seen in ventricular septal defect with "secondary" pulmonary hypertension. In the latter there is usually intimal proliferation of the small pulmonary arteries in addition to some degree of medial hypertrophy when the resistances are in the range calculated for this patient. The absence of intimal proliferation suggests a different pathogenesis between the pulmonary resistance in our case and the type seen in ventricular septal defect ("secondary"). The thickness of the media compared to the total vessel size is greater in this patient's left lung than in normal newborns. The total pulmonary resistance of 2585 dynes sec. cm.$^{-5}$ obtained at the first cardiac catheterization is comparable to normal newborn resistances. However, the finding of an increased resistance of 6200 dynes sec. cm.$^{-5}$ at 13 months of age indicates that this is a progressive phenomenon and therefore represents more than a mere persistence of normal medial hypertrophy of the newborn.

Even though the patient was over one year of age at the time of death, the finding of a closed foramen ovale suggests an interesting possibility. If the foramen ovale closed prematurely, from days to weeks prior to birth, it would be expected that the left atrium and mitral valve would not be as large as normal because of diminished flow into this chamber through this normal fetal passage. Thus, a relative mitral stenosis would be created. This, however, might be minimal enough so that it would not be easily measured or observed by routine measures (in our specimen, the mitral valve was slightly smaller than normal, but was not stenotic). Similar pulmonary pathology has been noticed in mitral stenosis patients. A combination of twice the normal pulmonary flow plus some degree of mitral obstruction might more readily account for the pulmonary pathology observed in this patient.

Dammann and Ferencz[27] described the lung findings in McKim and Wiglesworth's case of "Eisenmenger complex" with absent left pulmonary artery.[15] The small pulmonary vessels were thick walled in the right lung (lumen-wall ratio of 2.6) and thin walled in the left (ratio of 5.8). In this case, the right lung was said to be under the stress of a common ejectile force. No physiological data were obtained, and therefore it is difficult to make comparisons with our case. However, because of the presence of a ventricular septal defect in their patient, we assume that there may have been some degree of "secondary" pulmonary hypertension.

Surgical Aspects

In our case, because of the presence and progression of pulmonary hypertension, it was considered inadvisable to remove the lung on the involved side. In retrospect, inasmuch as this case appeared to have normal hilar and intrapulmonary vessels on the involved side, it would have been possible to do surgical correction or alleviation by making an anastomosis between the hilar portion of the right pulmonary artery and the main pulmonary artery by means of an arterial graft. This same conclusion holds true both for cases of isolated absent pulmonary artery and for cases associated with tetralogy of Fallot. In the latter instance it will be important to be prepared at the time of corrective surgery to bridge the interrupted portion of the artery with a graft. Actually, one of our recent surgical cases was a four year old boy having a tetralogy of Fallot defect with left aortic arch and absent left pulmonary artery. At surgery, the ventricular septal defect was closed and the infundibular pulmonary stenosis corrected. The patient died and on routine autopsy no left pulmonary artery was identified. In view of the findings of McKim and Wiglesworth[15], later examination was done, and this showed a blind pouch, 4 millimeters in diameter, corresponding to the hilar end of the pulmonary artery system; it gave rise to the normal system of pulmonary artery branches, and was connected proximally to a small occluded vessel which was undoubtedly a fibrosed ductus arteriosus.

Whether the above contemplated surgery would have helped in our case, or whether it is ever indicated in the usual case of isolated absent pulmonary artery remains problematical. It seems likely that the pulmonary stump or pouch at the hilus is about as large at birth as it will ever become, and thus surgery if it is to be done at all, perhaps should be done in infancy. Maier[14] suggested that in one of his cases of absent right pulmonary artery with an anomalous vessel from the aorta supplying the lung, the proximal end of this anomalous vessel could have been transferred to the side of the main pulmonary artery. From the autopsy findings, this case would seem to be different from the usual case of absent pulmonary artery, resembling the "ectopic" pulmonary artery of Frantzel's case already described.

SUMMARY

Congenital absence of the right pulmonary artery is described in a male infant with pulmonary hypertension. Gross and microscopic pathological findings are presented, as well as cardiac catheterization data and angiocardiographic findings. A theory is presented which appears to explain all variations of absent pulmonary artery. It is suggested that a more accurate term for this defect would be "proximal interruption of pulmonary arch." There is reason to believe that this condition is surgically correctable by means of an arterial graft.

RESUMEN

La ausencia congénita de la arteria pulmonar izquierda se describe en el caso de un niño con hipertensión pulmonar. Se presentan los hallazgos

macro y microscópicos así como los datos de angiocardiografía y cateterización cardiaca.

Se muestra una teoría que parece explicar todas las variaciones de la arteria pulmonar ausente. Se sugiere que se use un término más exacto para este defecto, el que sería "interrupción proximal de un arco pulmonar." Esta es una razón para creer que este defecto puede corregirse por injerto arterial.

RESUME

L'auteur décrit l'absence congénitale d'artère pulmonare droite, chez un bébé du sexe masculin atteint d'hypertension pulmonaire. Il présente les constatations anatomo-pathologiques macro- et microscopiques, ainsi que les résultats du cathétérisme cardiaque et les constatations angiocardiographiques. L'auteur expose une théorie qui semble pouvoir expliquer l'absence d'artère pulmonaire quel qu'en soit le degré. Il suggère qu'un terme plus précis soit adopté pour désigner cette altération, et qui pourrait être "interruption proximale d'un arc pulmonaire." Il y a des raisons de croire que cet état peut être corrigé chirurgicalement au moyen d'une greffe artérielle.

ZUSAMMENFASSUNG

Beschreibung eines angeborenen Fehlens der rechten Pulmonal-Arterie bei einem männlichen Kind mit pulmonalem Hochdruck. Makroskopische und mikroskopische pathologische Befunde werden vorgelegt, ebenso wie Herzkatheterwerte und angiografische Befunde. Es wird eine Theorie entwickelt, die alle Variationen des Fehlens der Pulmonal-Arterie erklärt. Es wird angeregt, dass eine genauere Bezeichnung für diesen Defekt gegehen wäre mit "proxymaler Unterbrechung eines pulmonalen Bogens." Es ist Grund vorhanden anzunehmen, dass dieser Krankheitszustand chirurgisch mittels einer Arterienplastik behoben werden kann.

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Circulatory Changes Associated with Inspiratory Positive Pressure Treatment*

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In the past decade there has been increasing application of positive pressure in the administration of oxygen therapy in the management of asthma and emphysema, as well as other conditions in which it was considered that this form of therapy might be of benefit. The present study is limited to the application of positive pressure during the inspiratory phase of the respiratory cycle.

Two types of apparatus were used, the Emerson Respiration Assistor,† and the Bennett Pressure Breathing Unit (Model TV-2P). These two appear to be similar in the amount of inspiratory effort required to evoke air flow under positive pressure, and in the readiness with which this flow is interrupted by the increased intrapulmonary resistance at the end of inspiration, permitting normal expiration to take place.

A variety of opinions exists concerning the benefits of IPPB provided with this equipment. Some of the leading proponents of this form of treatment have been Gordon,[1] Motley,[2] Trimble,[3] and Segal.[4] Examination of the publications of Motley shows that changes in pulmonary function produced by treatment provided with Bennett equipment cannot be shown to be of statistical significance. Segal[4] has shown that the use of IPPB, using Bennett equipment, without the aid of a bronchodilator actually brings about a reduction in vital capacity, timed vital capacity, and maximum breathing capacity. However, when the use of a bronchodilator is combined with IPPB, the performance of these tests exceeds that observed following the use of a bronchodilator alone when the latter is provided with a hand nebulizer. Other workers[5] have shown that no difference can be demonstrated between the benefits of an effective bronchodilator, nebulized with a pump or an oxygen tank, and the results obtained when IPPB is added to the routine.

This study is not an attempt to mediate between the different points of view presented above. It is concerned only with the circulatory changes associated with alterations in intrathoracic pressure which result from IPPB.

Of fundamental importance to the behavior of the heart is its degree of filling in diastole. This subject has been clearly presented by Wiggers[6] in his studies on Starling's law of the heart. These studies show the fundamental dependence of the heart upon the blood reaching it through the great veins of the thoracic cavity. Filling of the veins of the thorax, like the filling of veins everywhere, is a passive phenomenon, governed by the

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†Made available through the courtesy of J. H. Emerson Company, Cambridge, Massachusetts.

pressures and forces surrounding them. The forces associated with the respiratory effort are of great importance in this area. During inspiration, as the intrathoracic pressure becomes lower than that within the abdominal cavity, the neck, and the upper extremities, blood is forced into the chest. This process is promptly slowed during expiration as the intrathoracic pressure rises. In individuals with severe asthma or emphysema, who must carry out something approaching the Valsalva maneuver with each expiratory effort, no blood can enter the chest during this phase of respiration. It is to be expected that significant changes will take place when these individuals are subjected to IPPB. Mixter[7] has shown that inspiration augments the return flow of blood of the inferior vena cava in anesthetized dogs. Bjurstedt and co-workers[8] have shown marked lowering of the systemic blood pressure during exposure of anesthetized dogs to elevated intrapulmonary pressures of 40 cms. of water for periods of 15 seconds. Direct measurements in the superior vena cava were shown by Brecher and Mixter[9] to indicate increased venous return during inspiration, reduced by IPPB in the closed chest of anesthetized dogs. It has been stated by Whittenberger[10] that, while venous return is initially decreased, there occurs a rise in peripheral venous pressure which reconstitutes the venous gradient thus re-establishing venous return. It is considered by him, therefore, that venous return and cardiac output are only momentarily decreased because the reconstitution of a normal venous gradient maintains a normal cardiac output during positive pressure breathing. It is warned, however, that individuals in shock or impending shock, who are not capable of achieving a compensatory rise in venous pressure, may indeed suffer a significant drop in cardiac output.

Because of the increasing acceptance of this form of treatment, it was considered advisable to investigate further the influence of IPPB upon the circulation utilizing the dye dilution technique developed by Stewart[11] and

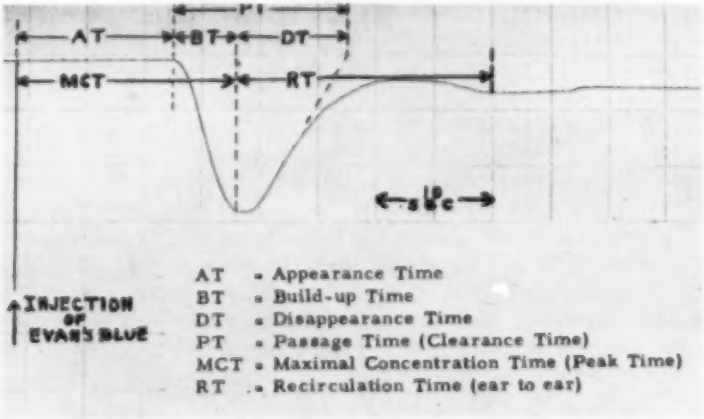

FIGURE 1: A dye dilution curve obtained by injecting .025 gm. of Evans Blue dye into the superior vena cava. The curve was registered with an ear oximeter and Leeds & Northrup recorder. The nomenclature of the features of this curve is indicated.

Hamilton,[12] and recently simplified by Wood and co-workers[13, 14, 15] using a recording oximeter. This technique has been shown by these and other workers[16] to be useful in estimating with considerable accuracy the cardiac output and flow rates through any channel studied by suitable techniques.

Technique Employed. Nine patients were studied. Three had unresolved pneumonia. Two had asthma. The remainder had pulmonary emphysema. Of these, two had severe cor pulmonale. All work was done with the patient in the semi-recumbent position in a quiet room at 7:00 A.M. before meals and other ward procedures could influence the circulatory status of the patient. With a B.L.B. mask 100 per cent oxygen was inhaled during the procedures in which a basal dye dilution curve was obtained and again during the administration of IPPB. This precaution was considered advisable in order to eliminate the influence of any degree of anoxia and to guarantee a steady base line in the record. Medication was eliminated from the apparatus during IPPB to avoid the possible influence on the circulation of the drugs commonly used. However, moisture was continually provided. The injection of dye was carried out as closely as possible at exactly five minutes from the time of onset of IPPB. The equipment used was the single scale ear oximeter developed by Earl Wood.* This was used in conjunction with a Leeds & Northrup Speedomax, Type G, amplifier and recorder. The latter was adjusted to a speed of 2.5 mm. per second. The oximeter ear piece was checked each time before use with filters of known transmission to insure correct operation. The dye used was Evans Blue,** which has been found suitable because of the fact that the light absorbed by it was maximal at a wave length of 620-630 mμ, which lies in the red range of the photocell filter in the ear piece. This photo-cell responds to changes in concentration of oxyhemoglobin which transmits light maximally in this range. When oxygen saturation is kept constant, therefore, changes in transmission in this area represent changes in light absorbed by Evans Blue dye.[13] Hence, transmission becomes a function of the concentration of Evans Blue. A constant quantity of dye (.025 gm.), dissolved in 5.00 ml. of water was used, injected with the identical number 18 needle and syringe, in order to avoid any variability from this source. Injections were made as rapidly as possible, ordinarily accomplished in less than a second, into an antecubital vein. A single pair of injections was carried out by way of a number 18 needle into a polyethylene catheter which had been previously introduced into the superior vena cava. The dye in these injections was immediately flushed through the catheter with 5.00 ml. of saline through a side adapter.

Results Obtained. The results obtained can best be interpreted using the terminology employed by Broadbent and Wood[16] as illustrated in Figure 1. Here is shown a dye dilution curve obtained when .025 gm. of Evans Blue was injected into the superior vena cava through a polyethylene catheter. The nomenclature adopted by Wood and his co-workers is provided.

*Manufactured by the Waters Corporation, Rochester, Minnesota.

**Supplied through the courtesy of the Warner-Chilcott Laboratories, Morris Plains, New Jersey.

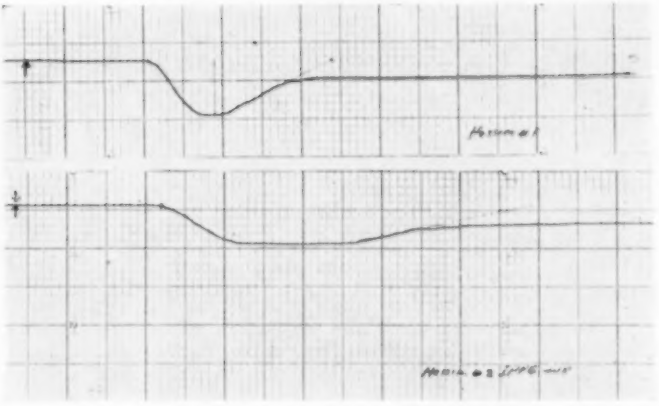

FIGURE 2: Upper tracing is a dye dilution curve obtained in a 55-year-old male while breathing 100 per cent oxygen. Lower tracing was obtained breathing oxygen with IPPB at + 18 cms. of water inspiratory positive pressure. Flattening of the curve with marked prolongation of appearance time, build-up time, and disappearance time is noted. A step-like return of the curve to the base line is noted. Vertical lines represent one second intervals.

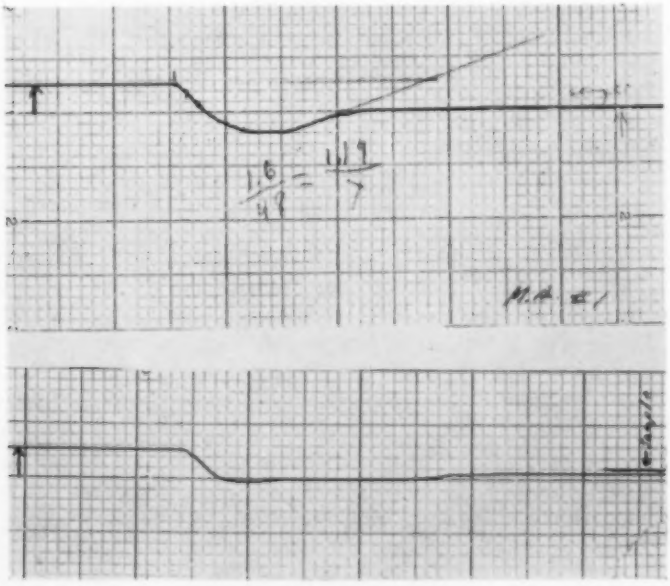

FIGURE 3: Upper tracing is a dye dilution curve in a woman of 35 breathing 100 per cent oxygen. Lower curve was obtained while breathing oxygen at + 18 cms. of water IPPB. Prolongation of appearance time, disappearance time, and passage time are noted, with marked flattening of the curve. Vertical lines represent one second intervals.

It was noted that the contour of the curves obtained by the technique utilized differed somewhat from those obtained by injection of the dye into the superior vena cava. The recirculation time was not detectable. Furthermore, the contour underwent profound changes under the influence of IPPB. No attempt was made, therefore, to utilize the curves for the estimation of cardiac output.

Three examples of these changes are presented. Figure 2 shows the changes undergone in a 55-year-old man with asthma who was given oxygen under a pressure of +18 cms. of water during inspiration with Bennett equipment. Flattening of the curve with marked prolongation of appearance time, build-up time, and disappearance time is noted. A step-like return of the curve to the base line is noted. Blood pressure dropped from 170/110 to 146/94 in 10 minutes.

Figure 3 shows the changes undergone in a woman of 35 with unresolved pneumonia of the left lower lobe, given oxygen at +18 cms. of water with Bennett equipment. The changes noted are similar to those noted in Figure 2. Blood pressure dropped in ten minutes from 110/70 to 70/60.

Figure 4 shows the changes in a 48-year-old man with unresolved pneumonia of the right upper lobe. He was given oxygen at +18 cms. of water with Emerson equipment. The prolongation of appearance time, build-up time, and disappearance time is striking. His initial pressure was 140/90. At six minutes, the patient indicated that he had a headache. His blood pressure was recorded at that time as 90/80. At eight minutes, his pulse and blood pressure disappeared, and the experiment was quickly terminated.

The detailed observations in all nine cases studied are listed in Table I.

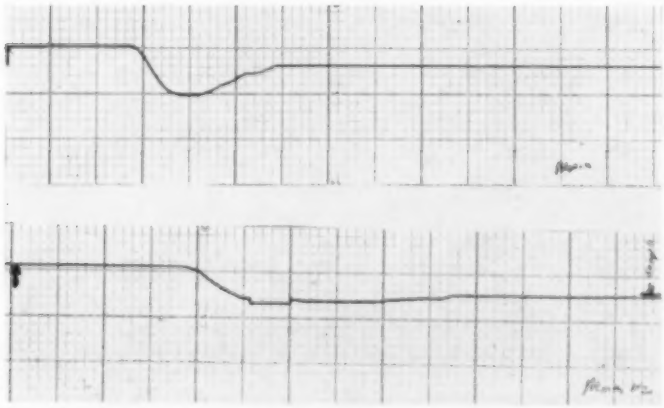

FIGURE 4: Upper tracing was obtained in a 48-year-old man breathing 100 per cent oxygen. Lower curve was obtained while breathing oxygen at + 18 cms. of water IPPB. There is striking prolongation of appearance time, build-up time, and disappearance time. An artifact due to jarring of the pen is noted at the peak of the build-up portion of the lower curve. Treatment was terminated at eight minutes because of disappearance of pulse. Vertical lines represent one second intervals.

TABLE I

DETAILED OBSERVATIONS IN EACH OF NINE CASES STUDIED

	AT 10-20	BT 7-15	DT 9-26	PT 15-35	MCT 16-35	RT 16-28	B. P. Average
Cases							
P. H. (Asthma							
Basal Figures	15.5	7.5	19	26.5	23.0	....	170/110
IPPB Figures + 18 cms. (Be)	17.5	11.0	34	45	28.5	....	146/94 at 10 min.
T. H. (Cor pulmonale)							
Basal Figures	12.5	6.0	15.5	21.5	18.5	....	108/68
IPPB Figures + 18 (Em)	14.5	5.0	20.0	25.0	19.5	....	90/68 at 10 min.
L. M. (Unresolved pneumonia)							
Basal Figures	13.5	5.5	12.0	17.5	19.0	....	140/90
IPPB Figures + 18 (Em)	19.0	8.0	41.0	49.0	27.0	....	0 at 8 min.
J. H. (Asthma)							
Basal Figures	10.0	6.0	20.5	26.5	16.0	....	108/78
IPPB Figures + 10 (Be)	15.5	8.0	20.0	28.0	23.5	....	106/84 at 10 min.
T. H. (Cor pulmonale)							
Basal Figures	21.5	10.0	27.0	37.0	31.5	....	108/68
IPPB Figures + 10 (Em)	27.0	8.5	42.0	50.5	35.5	....	90/68 at 10 min.
J. C. (Emphysema)							
Basal Figures	13.5	11.0	17.0	28.0	24.5	....	110/60
IPPB Figures + 5 (Em)	18.5	13.0	33.0	46.0	31.5	....	92/80 at 10 min.
M. A. (Unresolved pneumonia)							
Basal Figures	12.5	7.0	15.0	22.0	29.5	....	110/70
IPPB Figures + 18 (Be)	15.0	6.0	60.0	66.0	31.0	....	70/60 at 10 min.
N. G. (Emphysema)							
Basal Figures	14.0	5.0	13.0	18.0	19.0	....	104/70
IPPB Figures + 18 (Em)	16.5	5.5	16.0	21.5	22.0	....	90/60 at 10 min.
C. T. (Unresolved pneumonia)							
Basal Figures	13.5	5.0	10.5	16.0	19.0	....	100/68
IPPB Figures + 18 (Em)	18.0	8.5	16.5	25.0	26.5	....	94/66 at 10 min.

Figures indicate seconds.

AT—Appearance Time
BT—Build-up Time
DT—Disappearance Time
Be—Bennett equipment
RT—Recirculation Time
MCT—Maximum Concentration Time
RT—Recirculation Time
Em—Emerson equipment

These results are further analyzed in Table II.

TABLE II

ANALYSIS OF OBSERVED DATA

Total Cases—9	Unresolved pneumonia	3
	Asthma	2
	Emphysema	2
	Cor pulmonale	2
	Pressures applied during inspiration +5 to +18 cms. water	
Appearance Time	Uniform prolongation: 2 to 5.5 seconds; average 4.0	
Build-up Time	6 showed increase from .5 to 3.5 seconds; average 2.3 3 showed decrease from .5 to 1.5 seconds	
Disappearance Time	8 showed increase from 3 to 45 seconds; average 17.1 One showed decrease to .5 seconds	
Passage Time	All showed increase from 1.5 to 44.0 seconds; average 15.8	
Maximum Concentration Time	All showed increase from 1.0 to 8.0 seconds; average 5.0	
Blood Pressure	Changes in systolic level from 2 to 34 mm. Changes in diastolic level variable Changes in pulse pressure: uniformly lowered One patient in shock at 8 minutes	

SUMMARY AND CONCLUSIONS

A study of circulatory changes associated with Inspiratory Positive Pressure Breathing (I.P.P.B.), has been carried out in nine patients. Inspiratory positive pressure varying from +5 to +18 cms. of water was provided with Emerson and Bennett equipment. In every case, there was a drop in pulse pressure due to lowering of the systolic level and variable changes in the diastolic level. In one case, the blood pressure and pulse disappeared at eight minutes. Dye dilution curves were obtained as closely as possible at five minutes from the onset of IPPB. These showed marked alterations in all recognizable features when compared with previous curves obtained while inhaling 100 per cent oxygen. There was uniform delay in appearance time, passage time, and in maximum concentration time in every case, with prolongation of build-up time and disappearance time in most cases studied. The portion of the curve returning to the base line showed, almost invariably, a step-like appearance suggesting intermittent dilution of the bolus of dye by successive streams of blood entering the circulation in place of the smooth return ordinarily noted. The total picture adds up to a profound disturbance in intrathoracic circulation resulting from this treatment.

Under the circumstances, it is felt that this form of treatment should be provided only when indications for its use are clear-cut; and when used, continuous close observation of the patient is essential.

RESUMEN Y CONCLUSIONES

Se ha hecho un estudio de los cambios circulatorios que se asocian al uso de los aparatos de presión inspiratoria positiva (IPPB) en nueve enfermos. Las presiones positivas inspiratorias que varían de +5 a +18 cms. de agua ce aplicaron con los aparatos de Emerson y Bennett.

En todos los casos hubo una caída de la presión arterial debida al descenso del nivel sistólico y cambios variables en el nivel diastólico. En un caso la presión arterial y el pulso desaparecieron a los ocho minutos. Las curvas de dilución de colorante se obtuvieron tan exactamente como posible a los cinco minutos de empezarse a usar el IPPB. Estas curvas mostraron marcadas alteraciones en las características reconocibles cuando se compararon con las curvas previas obtenidas durante la inhalación de oxígeno a 100 por ciento. Hubo retardo uniforme en el tiempo de la aparición, tiempo de paso, y tiempo de concentración máxima en todos los casos con prolongación del tiempo de levantamiente y de desaparición en la mayoría de los casos estudiados.

La parte de la curva al volver a la línea basal mostró casi invariablemente una apariencia de escalones sugiriendo una dilución intermitente del bolo de colorante por corrientes sucesivas de sangre que entraban en la circulación en lugar del retorno uniforme ordinariamente observado.

El cuadro en conjunto se agrega al trastorno profundo de la circulación intratorácica que resulta de este tratamiento.

Bajo estas circunstancias se cree que esta forma de tratamiento debe darse sólo cuando las indicaciones para su uso sean precisas; y cuando se use hay que observar al enfermo muy cuidadosamente.

ZUSAMMENFASSUNG UND SCHLUSSFOLGERUNG

Es wurde an 9 Patienten eine Untersuchung der Kreislaufveränderungen vorgenommen, die mit der inspiratorischen positiven Druckatmung (IPPB) verknüpft sind. Der inspiratorische positive Druck, variierend von +5 bis +18cm Wasser wurde mit der Ausrüstung nach Emerson und Bennett erzeugt. In jedem Fall bestand ein Abfall des Pulsdruckes infolge Verringerung des systolischen Druckwertes und schwankenden Veränderungen des diastolischen Wertes. In einem Fall verschwanden Blutdruck und Puls nach 8 Minuten. Farbstofflösungskurven wurden sobald wie möglich gewonnen 5 Minuten nach dem Beginn der IPPB. Diese zeigten ausgeprägte Veränderungen in allen erkennbaren Merkmalen im Vergleich mit vorausgegangenen Kurven, die unter Inhalation von 100%-Sauerstoiff gewonnen wurden. Es bestand einheitlich eine Verzögerung in Zeitpunkt des Auftretens, der Passagezeit und der Zeit der maximalen Konzentration in jenem Fall mit Verlängerung der Aufbauzeit und Verringerung der Auflösungszeit in den meisten der untersuchten Fälle. Der sich zur Ausgangslinie zurückwendende Abschnitt der Kurve zeigte fast unveränderlich ein schrittweises Auftreten, das die Vermutung einer intermitierenden Lösung der Farbstoffpartikel erweckte infolge succesiven Eintretens des Blutstromes in den Kreislauf anstelle der gleitenden gewöhnlich beobachteten Rückkehr. Der Gesamteindruck rundet sich ab zu einer eingreifenden Störung der intrathorakalen Zirkulation als Folge dieser Behandlung.

Unter diesen Umständen hat man das Empfinden, als sollte diese Art der Behandlung nur angewnadt werden, wenn klare Indikation für ihren Ein-satz bestehen. Wird sie angewandt, ist fortlaufende Beobachtung des Kranken wesentlich.

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The Treatment of Chronic Coronary Heart Disease

The terms angina pectoris, coronary heart disease, heart pain, and coronary insufficiency will be used synonymously and interchangeably throughout this article. We shall define angina pectoris as that distress which occurs whenever there is a disproportion between the oxygen need of the myocardium and the oxygen being supplied to the myocardium at that particular moment. It becomes obvious that there are many conditions which may produce angina pectoris, for example:

1. Actual disease of the coronary arteries, such as arteriosclerosis, etc.
2. An inability of the blood to carry oxygen to the heart muscle such as occurs in chronic anemias, pernicious anemia, chronic carbon monoxide poisoning, etc.
3. A failure of the filling of the coronary arteries as may occur in severe aortic and/or mitral stenosis.
4. A physiological interference of the filling of the coronary arteries as is seen in the paroxysmal arrhythmias, etc.
5. Alterations in the mean aortic blood pressure as is found in aortic insufficiency.
6. A disproportion between the blood vessel supply and the muscle bulk of the ventricle as is seen in severe myocardial hypertrophy.
7. Lastly there are many instances in which no definitive cause can be found to explain the patient's pain.

The diagnosis is made by history alone. The patient states that as a result of physical effort or emotional excitement he sustains some type of pain somewhere in his body which is relieved by rest and/or by nitroglycerin. There is no laboratory test or physical finding that is pathognomonic of angina pectoris.

The patient suffering from this disease must have a complete history as well as a thorough physical examination, complemented and supplemented by all indicated laboratory procedures. In addition we would suggest that routine gall bladder and complete gastro-intestinal x-ray examinations be done as well as studies of thyroid function.

Treatment of Angina Pectoris

This discussion will be limited to our personal treatment in coronary heart disease. The treatment of angina pectoris must be, first of all, the treatment of all concomitant diseases that may be present. They may be treated simultaneously with the treatment that is directed to relieve the coronary pain. Often the correction of an anemic condition, relief of a hyperthyroid state etc., can greatly reduce the number of anginal seizures.

Our Treatment for Chronic Coronary Heart Disease Depends Upon Education

By education we mean the explanation to the patient and to his closest relative the nature of coronary disease. We relate all pertinent information both to the individual and his closest relative. It has been our experience that the patient and his family appreciate understanding the nature of this disease. The patient must be reassured that the diagnosis does not connote either sudden or impending death. He must be constantly reassured that people with this disease can and are able to live a normal or nearly normal life. It is emphasized that any restriction in his activity is the result of the disease itself. The activity or limitation of activity placed upon the patient should be judged entirely by the patient's symptoms. We ourselves place no limitation upon the patient. The physician and the patient seek through trial and error to find those adverse things that may produce pain. We discuss with the patient any restrictions that are necessitated by this trial and error method, and select the course best suited for the individual to carry on his life. We teach the patient to live within his pain or cardiac reserve.

Drugs

Anticoagulants: We do not use anticoagulants routinely. We restrict their use to those individuals who have had repeated myocardial infarctions, frequently recurring anginal attacks, previous embolic phenomena, or who have some extra cardiac condition indicating their need. We use dicumarol in individual daily doses in a strength that will maintain a prothrombin activity of between 20 and 30 per cent of normal. This must be determined empirically.

Atropine Sulfate: Atropine sulfate is used in doses of gr. 1/200 or 1/150. It is frequently used for post-prandial anginal distress. Our favorite prescription is:

Calcium Carbonate	gr. V
Magnesium Oxide	gr. V
Bismuth Subnitrate	gr. V
Atropine Sulfate	gr. 1/150
Sodium Phenobarbital	gr. ss
Soda Bicarbonate q s	gr. xxx

Directions: The patient takes one powder tid pc and also at bed time if needed.

Digitalis: Digitalis is indicated in the presence of heart failure. We still use the whole leaf form and restrict the glycoside for rapid digitalization. We have selected digitora as the product of our choice. The grains 1.28 tablet is for practical purposes one cat unit. The patient is digitalized by giving one cat unit for every 10 pounds of body weight in divided doses over a period of about one week. Once digitalization is completed the effect of the digitalis is maintained by a maintenance dose. This usually is one cat unit daily. Digitoxin is used orally for rapid digitalization with a total of 1.2 mg. being the average digitalization dose. The maintenance

dose varies from .1 to .2 mg. daily. If the patient is vomiting we use Cedilanid intravenously, 8 cc. of the drug being the usual digitalizing dose and the maintenance dose varying from two to four cc. daily.

Diuretics: The prophylactic use of a diuretic in conjunction with digitalization will often relieve the patient of "Nocturnal Angina." We use Salyrgen Theophylin in a dosage of 1 cc. intramuscularly as often as is needed to yield the desired therapeutic effect.

Iatrogenic Hypothyroidism: The creation of various degrees of hypothyroidism has been suggested for the treatment of severe coronary or intractable angina pectoris. We seldom use this form of therapy. It is our belief that there are very few individua'ls suffering from "intractable angina." We feel that in all likelihood we are dealing with an "intractable patient" with angina rather than an "intractable angina." The hypothyroidism may be instituted by surgical removal of the thyroid gland, by the use of anti-thyroid drugs such as propylthiouracil or fractionated doses of radio-active iodine. Surgery and x-ray irradiation are seldom used. At the moment radioactive iodine is most popular.

Nitroglycerin: We depend on nitroglycerin for the treatment of angina pectoris. The patient is taught to use the drug therapeutically and prophylactically. The average doses varies from gr. 1/200 to gr. 1/100. The patient places the tablet under his tongue and as soon as it is dissolved there is relief of pain. We suggest that the patient should use the tablet at the onset of his pain and not wait until the pain is fully developed. If the patient must perform some act which he knows from previous experience will produce pain we suggest he take the nitroglycerin tablet before he performs the act. We rarely use any other treatment for the acute attack.

Quinidine Sulfate: This drug is used both therapeutically and prophylactically to control the arrhythmias. The dose is gr. 3 four times daily or every four hours "around the clock." The individual dose is increased gradually until the desired therapeutic effect is obtained, then the effect is maintained by a maintenance dose.

Sedatives: These are used when indicated and we have a preference for mebarol gr. 3/4 q.i.d. Patients are usually not familiar with this drug and do not confuse it with phenobarbital.

Surgery: A surgical procedure that is indicated can be performed safely in patients with coronary heart disease. Many times the removal of a diseased gallbladder etc., will diminish the number of anginal attacks. We know of no contraindication to surgery in the patient with chronic coronary disease. It is essential, however, that one have the anesthesia administered by a trained anesthesiologist.

Surgical procedures relative to the relief of coronary artery pain or as an attempt to revascularlize the heart are many. We do not recommend any surgical procedure for the treatment of angina pectoris. It is our belief that any results obtained are psychological and not physiological.

Tranquilizers: The tranquilizers are used only if indicated. May we suggest that the patient should be constantly observed for the side effects

that can occur from the use of these drugs and particularly bizarre and unusual psychotic reactions.

Usurp

To usurp means to "use without authority." Too often physicians without proper reason will elect to restrict and regulate the life of patients. This self-appointed dictatorial approach in the treatment of angina pectoris is totally unwarranted.

Coitus

If the patient has no pain or anginal distress during or after coitus no restrictions or suggestions are needed. Occasionally a patient may develop impotence either because of the fear of the act or because he has experienced anginal pain during the act. In these instances reassurance and reeducation is necessary. In this event we suggest the pre-coital use of nitroglycerin which will often abolish the seizure. We also suggest that the normal partner take over the active role in the coital act. We advise the patient and his partner to discuss the problem with us should further difficulties arise.

Alcohol

We do not recommend or advise the use of alcohol in any form in the treatment of angina pectoris. It has no physiological effect on the coronary circulation and too often the patient develops a therapeutic enthusiasm that necessitates the change of treatment from angina to that of alcoholism. May we suggest at this time that we do not alter the patient's smoking habits unless smoking produces chest pain.

Tension

The individual is taught to avoid all forms of nervous tension and emotional fatigue. He is instructed particularly in avoiding emotional upsets, strain, worry or anger. The drugs outlined above may be used to assist the patient during this particular phase of his treatment. We frequently advise the reading of "How to Live 365 Days a Year" by Dr. Schindler. The patient may be referred to Group Therapy, if it is available in the community. We must spend time with the patient and his associates in overcoming the anxiety and fear he has concerning his disease, the anxiety and concern he has in regard to returning to normal activity, and, particularly, in overcoming the reactive depression in his illness.

Iatrogenic

The physician must be careful both in his actions and speech to avoid creating disability and fear in the victim of coronary heart disease. It is possible for the physician to transfer to the patient his own emotional immaturity and/or his lack of knowledge concerning the method of handling the victim of coronary heart disease. Should the physician find it difficult to handle the emotional factors in the patient's illness it would be better for the physician and the patient if the patient be referred to a physician so disciplined.

Optimism

Optimism is the watchword in the treatment of these patients. There is no room for pessimism and no room for unneeded and unwarranted re-

strictions in their life. It is the duty of the attending physician to constantly "preach the gospel of optimism." He must reinforce this optimism by indoctrinating this philosophy in the patient, his family and associates. He must return the patient to his job and to his place in society as quickly as possible. The *only restrictions* to be placed on the individual are those that arise in the limits of the area of his pain reserve or his cardiac reserve. He can do anything he wants to do as long as it does not produce distress. He may ride in planes as long as they are pressurized but he must not pilot a plane. Should he experience pain in anticipation of his flight or repeated pain during flight he should avoid air travel. He may drive his car if driving does not exasperate him. If, however, he experiences pain while he is driving he should pull to the side of the road and remain there until the attack of pain stops. The patient is taught moderation but not restriction. The patient is advised not to become over fatigued and not to do anything to excess. Rest periods are often of value to these people. He should avoid undue physical exertion particularly during inclement weather. The "optimism treatment" must be constant and in full doses.

Nutrition

Diet: If the patient has good eating habits and there is no indication for a special diet he receives no dietary instructions. If he has an allied disease that requires dietary management the indicated diet is furnished. If the patient is obese he receives a 1200 calorie diet which is supplemented by a daily multiple vitamin mixture. He remains on this routine until his weight is normal. Low sodium diets are administered when indicated. The low-fat or low-cholesterol diets are not prescribed unless they are indicated. If desired, one may also prescribe the proprietary preparations that assist in lowering blood cholesterol levels. The patient is taught to avoid overeating and overdrinking; to eat slowly and to chew his food well. Flatulence is relieved by the use of the powder above outlined and constipation is treated when present. The patient is taught not to strain at stool.

Summary

Our treatment of angina pectoris depends on:

1. Accurate diagnosis
2. The treatment of allied and concomitant diseases
3. EDUCATION of the patient, his family and his associates

CONCLUSION

We place no arbitrary restrictions on the victim of coronary heart disease. The only restrictions are those within his own pain or cardiac area. He is taught to live a normal life or as nearly normal life as it is possible for him to live. In our efforts to Add Years To His Life we must remember that in doing so we must be certain we are Adding Life To Those Years.

JOHN FRANCIS BRIGGS, M.D., F.C.C.P.*
and JAMES BELLOMO, M.D.
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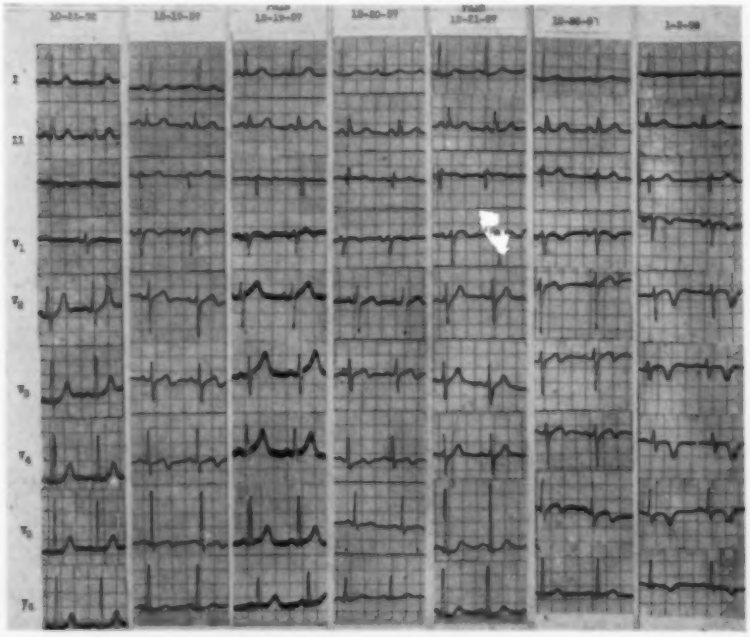
*Associate Professor of Clinical Medicine, University of Minnesota.

THE ELECTROCARDIOGRAM OF THE MONTH

The authors would be pleased to receive comment and controversy from readers in relation to explanation offered

A 59 year old man developed paroxysms of pain beginning in the right arm, and spreading to the right shoulder and the right lower jaw. During three of these attacks electrocardiograms were recorded that were entirely normal and identical to the tracing (October 22, 1952) made five years before the attacks began. No electrocardiograms had since been made in the absence of pain. Accordingly, when he was first seen by one of us (M.G.) an interim tracing (December 19, 1957) was made. Later on the same day a paroxysm of pain occurred during which another electrocardiogram (December 19, 1957 pain) was recorded. On the following day another interim record was made. On December 21, 1957 another attack of pain occurred.

In this case the electrocardiograms were normal during attacks of pain, and abnormal in the interim. Viewed superficially this is the opposite of what occurs in most cases of angina pectoris so that this phenomenon has been dubbed "parodoxical." Actually it is not parodoxical at all. The explanation is rather simple. Several attacks of angina had left a degree of "ischemia" presumably in the epicardial layers of the anterior wall of the left ventricle, as evidenced by the terminal inversion of the T waves in the precordial leads of the interim tracings. During an attack of angina, if and when the classical injury effects occur in the epicardial layers of the anterior wall of the left ventricle, the RS-T segments (and usually also the T waves) of the precordial leads are displaced upward. In this case, as they not infrequently do, they reverse the direction of the previously inverted T waves (of the precordial leads). In short, as in any case, the electrical effects of the current of injury are in a direction opposite to that of the electrical effects of ischemia in the same zone. In most cases of angina the affected zone seems to be endocardial.



Under this circumstance the current of injury results in *downward* shifts of the RS-T segments in the precordial leads and if a degree of ischemia is left after the attack the T waves are *increased* in height (in contradistinction to the effect of epicardial involvement). Since even large increases in the height of the T waves of the precordial leads cannot often be recognized as abnormal, the electrocardiogram is "normal" between attacks and shows abnormality (RS-T shifts) only during the attacks. Thus the so called "parodoxical" events shown in Figure 1 are simply determined by the fact that the affected area is in the epicardial zone rather than in the more usual endocardial zone. The smaller R waves in the anterior and left precordial leads in the last record suggest that some infarction has occurred but this was not confirmed by other laboratory findings. Variation in placement of the electrodes may account for this change.

The important practical point that is emphasized by this case is the following.

In the investigation of pain in the chest it is important to record electrocardiograms *during the attack*, but it is also important to record the electrocardiogram *between* attacks. Actually, having succeeded in gaining an opportunity to make tracings during or shortly after an attack of pain, *whatever* the appearance of that tracing, one should administer nitroglycerin and continue to make records at short intervals until the tracing ceases to change. It is the series of changes that is diagnostic.

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The Surgical Treatment of Tetralogy of Fallot*

Report of the Section on Cardiovascular Surgery
American College of Chest Physicians**

Since the introduction of the Blalock-Taussig systemic pulmonary anastomosis in 1945, the Potts-Smith aorticopulmonary anastomosis in 1946 and the Brock direct pulmonary valvulotomy in 1948, a significantly large group of patients suffering from the tetralogy of Fallot has been treated by these surgical methods. This experience has demonstrated clearly that in the majority of these individuals a great deal of benefit has been derived and that the postoperative mortality rates, early and late, have been reasonably low. A comparison of the results obtained by the three methods indicates that the overall results are not strikingly different. "Good" or "very good" results have been reported in roughly 75 per cent of cases, with mortality rates approximating 10 to 15 per cent.

Until recently, such beneficial results left little, if any, question regarding the advisability of recommending one of these operations even though the ideal of any surgical procedure, that is, complete correction of all of the defects present, admittedly was unattainable. However, recent progress in the development of the various cardiac by-pass techniques, which in most instances makes possible the ideal of complete correction of the defects, calls for reappraisal of the surgical indications.

In an attempt to establish the indications for the various procedures in view of our present knowledge, the Section on Cardiovascular Surgery of The Committee on Cardiovascular Disease of the American College of Chest Physicians sent questionnaires to the various members of its Advisory Committee throughout the world. Thirty-nine of the Committee members responded giving information based on their experience with a total of 4062 cases. Unfortunately, the questionnaires were answered in such a manner that in discussing many specific phases of the problem only a part of the total number of cases could be included. Still, many significant facts have been obtained which should be of definite help to us as physicians in properly advising the patients who come under our care.

Analysis of Results

1. *Operative Mortality Rates*

A comparison of the results obtained in a total of 2439 cases is given in Table I.

The total mortality rates for the different procedures were quite similar with the exception that resection of an infundibular obstruction when associated with the various open techniques was over twice that of the indirect methods. However, the results obtained with the open techniques must be given further consideration. As shown in Table II, the number

*Presented at the 24th Annual Meeting, American College of Chest Physicians, New York City, May 29-June 2, 1957.
**Compiled and prepared by W. R. Rumel, M.D., F.C.C.P., Salt Lake City, Utah.

TABLE I

OPERATIVE MORTALITY RATES (2439 CASES)

Number of Cases	Procedure	Deaths (Per Cent)		
		To 3 Months	Over 3 Months	Total
1497	Subclav.-Pul. Anast.	13.8	5.3	19.1
515	Aortic-Pul. Anast.	10.6	6.6	17.2
238	Pul. Valvulotomy	16.3	2.9	19.2
67	Infundibulectomy (Closed)	23.8	2.9	26.7
122	Open Repair	38.5	0.8	39.3

of cases reported by the various surgeons was of significant size in only two instances, being 54 and 48 respectively.

These two surgical groups reported over 80 per cent of the total of the 122 open procedures. The total mortality rate in the two averaged 28.4 per cent, which is definitely higher than that associated with the simpler techniques allowing for incomplete correction but which is not prohibitive in the developmental stages of a technique making possible complete correction of all of the defects present. A cardiac by-pass method was employed in 110 of the 122 open operations. One case was done under hypothermia and in the remaining 11 the technique was not specified. As is generally true in the development of any new technique, a significant decrease in the operative mortality rate has been reported by one

TABLE II

MORTALITY RATES
OPEN REPAIR-TECHNIQUE UNSPECIFIED (112 CASES)

Number of Cases in Group	Per Cent		
	To 3 Months	Over 3 Months	Total
54	25.9	1.8	27.7
48	29.1	....	29.1
2	50.0	....	50.0
5	100.0	....	100.0
4	100.0	....	100.0
3	100.0	....	100.0
2	100.0	....	100.0
1	100.0	....	100.0
1	100.0	....	100.0
1	100.0	....	100.0
1	100.0	....	100.0

group as experience with the method has increased. In 1955, the operative mortality rate in nine cases was 55 per cent; in 1956 in 28 cases, 28.5 per cent and up until May 1957, in 11 cases the rate was only 9 per cent. Although no conclusions can be drawn on such a short term follow-up, still the trend seems encouraging. In the remaining 20 cases, representing the early experience of nine different surgical teams from different areas, the mortality rate was 95 per cent, there being only one survivor. This points out vividly that the development and application of one of these technical methods should not be undertaken lightly by an individual or group of individuals, since obviously the risk to the patient in the early experience is exceedingly high. It also brings up another problem which is difficult or impossible to answer on the basis of statistics, but which most certainly should be given conscientious consideration before anyone embarks upon the task of developing one of these techniques. The question is: From a *practical standpoint*, how many such surgical units are really necessary in a given geographic area to handle adequately and safely the patients from this area who will require this type of highly specialized care? If a hypothetical geographical area had a maximum potential of 20 cases annually, then this area most certainly would not need three units and perhaps the interests of *all concerned* would be served better if no unit at all were set up, assuming, of course, that other workable arrangements could be made to provide the patients with the care they need. Other obvious ramifications of this question, which must be settled after adequate deliberation seasoned with practicality, concern physician and hospital competition and the moral responsibilities to patients of those providing medical care. This, in turn, brings up the question as to how many more cardiovascular surgeons are needed in our nation to best serve the interests of both the doctor and the patient. An answer is suggested by the surprisingly small total number of cases of the various surgical procedures reported by the members of the surgical advisory committee who are prominent surgeons in their respective geographical areas (Table III).

Since these cases have been done over a period of approximately 10 years one must be led to believe that the potential reservoir, numerically, is relatively small, particularly if resident training is included in our

TABLE III

NUMBER OF CASES REPORTED BY 22 MEMBERS OF SURGICAL ADVISORY COMMITTEE

Procedure	Number of Cases			
	Over 100	50 to 99	25 to 49	Under 25
Subclavian-Systemic Anast.	4	7	3	8
Aortic-Pul. Anast.	2	1	2	14
Pul.-Valvotomy	0	2	0	20
Infundibulectomy	0	0	1	9

TABLE IV
INCIDENCE OF RE-OPERATION

Number of Cases	Procedure	Re-Operated	
		No.	Per Cent
185	Subclav.-Pul. Anast.	16	8.6
58	Aortic-Pul. Anast.	2	3.4
106	Pul. Valvotomy	1	0.9
19	Infundibulectomy	4	21.0

thinking. Not only teaching hospitals but many large and even some small community hospitals have taken the attitude that whatever is being done elsewhere should be done within their halls also, especially if it is dramatic and likely to stimulate further community support. We cannot reasonably expect an automatic solution of the problems on the basis of the time honored law of supply and demand because in recent years this law has been rendered largely unreliable by distorting, powerful, artificial influences, most of which we, as physicians, have sponsored or have passively accepted.

Re-operation after failure of an initial procedure was reported as being necessary in 0.9 per cent of the valvulotomy cases, with increasing frequency in the other groups up to a maximum of 21 per cent in those treated by infundibulectomy (Table IV).

The indications for re-operation were incomplete relief of right ventricular outflow tract obstruction or inadequate systemic-pulmonary artery shunt.

II. *Results of Surgical Treatment*

Clinical results classified simply as "good" or "poor" were reported in 1681 survivors. Obviously, these descriptive terms are based upon the overall general condition of the patient and have no reference to future complications which probably will arise as a result of residual defects, any one of which may represent an indication for surgical correction (Table V).

Both shunt procedures gave essentially the same results, i.e., approxi-

TABLE V
CLINICAL RESULTS (1681 SURVIVORS)

Number of Cases	Procedure	Result (Per Cent)	
		Good	Poor
1041	Subclav.-Pul. Anast.	86.8	13.2
368	Aortic-Pul. Anast.	85.3	14.7
195	Pul. Valvotomy	79.4	20.6
37	Infundibulectomy	75.6	24.4
40	Open Repair	100.0	0

TABLE VI

OPERATIVE MORTALITY RATES (VARIOUS TECHNIQUES)

Age	Number of Cases	Deaths Per Cent
Under 14 Years	261	16.0
Over 14 Years	60	23.3

mately 86 per cent "good" and 14 per cent "poor." The direct operations on the stenotic valve or infundibulum produced somewhat less favorable results with approximately 78 per cent listed as "good" and 22 per cent "poor." It is interesting and encouraging to note that the one surgical group reporting 58 cases treated by an open operation indicated the attainment of "good" results in 100 per cent of the survivors. This would tend to dispel the fear that correction of the septal defect and removal of the right ventricular outflow tract obstruction at the same time might have an untoward effect on the pulmonary vasculature. Significant data were not obtained concerning the frequency of "good" and "poor" postoperative results, initially, one year later, and five years following surgery.

The effect of the patient's age on the results obtained was given in a small group of cases. The mortality rate in those over 14 years of age was somewhat higher (23.3 per cent) than it was in those below 14 (16 per cent) (Table VI).

While the clinical impressions of some reporting surgeons indicated that the clinical results were better in patients under 14 years of age, still in the 230 cases where percentages were given, good results actually were somewhat more common in the older age group (Table VII).

III. *Miscellaneous Data*

In 901 patients surviving surgery the incidence of subacute bacterial endocarditis or brain abscess was 1.5 per cent. This relatively high incidence of serious bacterial complications is another significant factor which must be considered during our deliberations on indications for surgical treatment.

The hematocrit, hemoglobin, or red blood cell count, returned to a normal range in only 23.3 per cent of 386 patients concerning whom this question was answered.

TABLE VII

CLINICAL RESULTS (VARIOUS TECHNIQUES)

Age	Number of Cases	Per Cent Good	Per Cent Poor
Under 14 Years	200	78	22
Over 14 Years	30	81	19

The absence of a pulmonary artery which could be used in establishing an adequate shunt was reported in 4.3 per cent of 1033 cases.

Discussion

Offhand, the results of the various surgical measures used in treating the tetralogy of Fallot would seem quite satisfactory, especially if attention is focused on the reported percentages of "good" results which average around 75 to 85 per cent. However, these percentages are based solely upon the condition of those surviving surgery and its complications. The patients who died during the operation or later were excluded. If a more critical and realistic analysis is made, one must conclude that an average patient subjected to one of the standard operations is not justified in anticipating an 80 per cent chance of a "good" result with a 20 per cent chance that the result will be "poor." Actually, he must face a risk of 10 to 20 per cent that he will die within three months of the operation; another 2 to 6 per cent chance that he will die within the next five years or so and an additional risk of 15 to 25 per cent that he will obtain a "poor" clinical result. This may arise from such complications as uncontrollable pulmonary hypertension, cardiomegaly, progressive cardiac decompensation and important postoperative alterations of intrapericardial anatomy, etc., part or all of which may be irreparable even by definitive surgery at a later date. In summary then, his chance of obtaining a "good" result would be 61 per cent with a 39 per cent chance that he will die or obtain a "poor" result.

The relatively favorable results now reported in cases treated by the open technique presumably will be duplicated or improved upon in the near future. Therefore, it would seem reasonable to postpone surgery of any type unless proved satisfactory facilities for the open operation can be made available at a reasonable operative risk. Even if such facilities are not available, perhaps the complete operation should be reserved solely for those patients who show evidence of deterioration in their general condition, or for those whose course is static, but whose general condition is poor. As further experience actually reduces the operative risk, the surgical indications may be extended to patients who are doing well clinically, if operative units providing satisfactory results are accessible. Unfortunately, for various reasons, units providing for safe open heart surgery are not available at present for most patients with the tetralogy of Fallot and perhaps will not be available in many areas for some time to come. Therefore, one of the standard incomplete operations should be advised in patients who are showing definite evidence of deterioration from a clinical standpoint, and in those whose general condition is intolerably poor.

Conclusions

1. This report concerns an analysis of the results obtained in the surgical treatment of 4062 cases of the tetralogy of Fallot by 39 members of the Advisory Committee of The Section on Cardiovascular Surgery of The American College of Chest Physicians.

2. Although "good" results were reported in approximately 80 per cent of the patients surviving the various standard operations, still patients submitting to these procedures are actually faced with a 39 per cent risk of death or a "poor" clinical result.

3. Complete open repair using cardiac by-pass techniques was reported by some as providing "good" results in most instances, with a total associated mortality rate approaching that of the standard incomplete techniques.

4. The operative mortality rate associated with open techniques, as reported by most surgeons, was 95 per cent. This indicates clearly that extreme caution should be exercised before any individual or group of individuals embarks upon the development and clinical employment of one of the cardiac by-pass techniques, and also indicates that the total number of these units in any geographic area should be kept as small as is practicable.

5. In view of the evidence at hand, it would seem advisable to postpone all types of surgery in patients with the tetralogy of Fallot whose general condition is not poor or deteriorating, unless a safe facility for cardiac by-pass and total correction of all the defects is available.

6. If the patient's general clinical condition is poor or deteriorating, cardiac by-pass with complete correction of the defects should be done if safe facilities are available, but if not, one of the standard incomplete operations should be performed.

Editorial

Biological Effects of Diagnostic X-rays*

For years increasing use has been made of radiologic examination of the chest both for individual diagnosis and for mass screening for disease as a means of protection of the community. As is not infrequently the case with a useful procedure, it may tend to be overdone. The Committee on Radiation Effects of the National Academy of Sciences called attention in the spring of 1956 to the amounts of radiation received by the gonads in the course of the diagnostic use of radiation and called attention to the fact that the total dose to the gonads was in some countries approaching a level of genetic significance to the race. Their findings were reviewed by the United Nations Scientific Committee on the Effects of Atomic Radiation which made in a statement distributed to medical journals the following significant points among others.

"The medical use of radiation is clearly of the utmost value in the prevention, diagnosis, investigation and treatment of human disease, but the possible effects of this irradiation of individuals require examination . . . the extent of such genetic radiation from diagnostic procedures has been found to be equal to at least 100 per cent of all natural radiation in two countries... The Committee is therefore anxious to obtain the help of radiologists in suggesting through appropriate governmental channels any methods by which this total exposure could be reduced and in estimating the amount of reduction that might be expected from any such methods. In particular it would be valuable to know how much the radiation to the gonads could be reduced."

That the fears of the geneticists are not entirely academic and that even the risk of somatic damage in some diagnostic procedures is real is evidenced by the following experience of a patient in a sanatorium in the United States. In one month he received diagnostic radiologic examinations that delivered to his skin and that portion of his bone marrow close to his skin a total of 70 r.

It is important that radiation be used with caution and economy of exposure, but it is equally important that we not allow such diseases as tuberculosis and operable cancer of the lung to be missed until they have become virtually incurable.

It should be remembered, particularly in the case of children, that skin testing for tuberculosis is in many communities a satisfactory mass screening method, only the positive reactors being subjected to x-ray examination.

The present estimate based on studies made for the National Academy of Sciences Radiation Committees is that males receive 1.2 milliroentgens in a diagnostic chest examination, females 0.3 milliroentgens. The effect on the gonads is cumulative, and there is no threshold, so any added radiation at the natural background radiation must be considered as damaging

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*From the Cancer Research Institute, New England Deaconess Hospital, Boston.

in slight degree. Geneticists have agreed that in general it is feasible for a population to receive an average dose to the gonads of 10 r up to age 30 in addition to the approximately 10 r that they have received during the same time from the natural background radiation. The level at which damage is done to bone marrow is as yet uncertain, but 15 r to the whole bory or to the bulk of the skeleton will produce transient though insignificant changes in the white blood cells. It is probable that the increased incidence of leukemia in radiologists is associated with an accumulated dose of close to 1000 r.

If each physician would ask himself before ordering a diagnostic procedure, "Is this really necessary," much unessential radiation could be avoided. At the same time the value of mass screening techniques for the detection of tuberculosis and other lesions of the lung is sufficiently high to regard a discontinuance or impairment of them as a public health disaster.

It is feasible to utilize x-rays safely but constant vigilance must be maintained to prevent unnecessary frequency of diagnostic examinations and undue exposure in the course of diagnosis.

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Tuberculosis Control in the Philippines and International Congresses

Our discussion of the campaign against tuberculosis in the Philippines inevitably concerns itself chiefly with local conditions. We feel that although the observations come from an isolated sector, they are not only of pathetic interest because of the extreme difficulties encountered and the heavy inroads which the disease makes on our poor community, but also because of their international implications. As has been said, "no nation is safe if another nation is vanquished by the disease." Tuberculosis has been for centuries the number one disease in this country and bids fair to continue so for many a decade yet to come.

The organized campaign against tuberculosis in the Philippines was initiated under the patronage of the Governor-General and other high government officials some 45 years ago, but it was largely promoted and maintained by private voluntary agencies, aided subsequently by fund-raising legislation, like the enactment of the Philippine Charity Sweepstakes. The campaign against tuberculosis is the longest sustained campaign and one of the greatest voluntary efforts against a single disease in the history of this country. This circumstance alone is of the greatest importance because it enhances community interest in health matters, particularly with reference to this number one disease, and the movement should be encouraged if only for that consideration. We are still far from being genuinely health minded.

Because of low economic conditions, it is almost a derision to speak of home or domiciliary treatment in the Philippines, if that term implies any sense of home adequacy. Serious efforts are being made in this direction, mainly because of highly inadequate hospital facilities. The homes of our poor are tiny one-room, or at best two-room affairs, where everybody in the household lives, moves about and sleeps, in sickness and in health. Remembering that it is not unusual for several families to constitute the Filipino household and that the average Filipino family is proverbially a large one, this gives an idea of the terrible exposure to which the many contacts are exposed. This is only to point out the difficulties and the scant results that can be expected from such measures. The educational efforts must therefore be continued with vigor and purpose.

When we read about the recent trends in the treatment of tuberculosis with emphasis on home or domiciliary treatment, we can only feel the bitterness and pathos of it in the light of our local conditions. Nothing radical can be accomplished in this direction until the overall economic status of our people materially improves. It will always remain an uphill fight to bring this about without seriously endeavoring to change the sense of values of our people by precept and example.

Another prolific source of spreading tuberculosis infection in our community is the fairly large number of public school teachers who, even though they are supposed to be x-rayed and screened before employment

and examined periodically during employment, are found to have advanced lesions after having taught for long periods, and exposing an average of 40 to 80 children daily, depending upon whether they have single or double sessions. The results stagger the imagination. In the case of private school teachers the situation is probably worse.

If these things happen with groups that are at a high instructional level, how much less satisfactory must be the conditions elsewhere. Furthermore, the problem of tuberculosis definitely calls for a more prominent place in the teaching in medical schools of this country.

These are instances of the inadequateness of attention given to the problem of controlling tuberculosis in this country. Voluntary agencies, such as the Philippine Tuberculosis Society, have definitely been helping the Government a great deal for many years and should be given the utmost encouragement and recognition.

In this connection, the personal contacts made at the International Congresses on Diseases of the Chest held in Rome, Rio de Janeiro, Barcelona and Cologne—like the First Pacific Conference on Tuberculosis which was held in Manila four years ago, and the XIVth International Union Conference on Tuberculosis held recently, in New Delhi, India—have been of incalculable value to tuberculosis workers in the Philippines. To these must be added the much sought for visits to this country by recognized authorities in the campaign against tuberculosis.

MIGUEL CANIZARES, M.D., F.C.C.P.*
Manila, Philippines

*Regent for the Philippines.

J. Winthrop Peabody, Sr., M.D.

DR. J. WINTHROP PEABODY, SR. RECEIVES 1958 COLLEGE MEDAL

Dr. J. Winthrop Peabody, Past President of the American College of Chest Physicians, was presented with the College Medal and Certificate of Award for meritorious achievement in the specialty of diseases of the chest at the annual meeting of the College in San Francisco, California, on June 21, 1958. The award was made by Dr. Burgess L. Gordon at the President's banquet held at the Fairmont Hotel.

The award was given in recognition of Dr. Peabody's unselfish devotion to the aims and ideals of the College since its foundation, but particularly to the advancement of postgraduate medical education. Since its inception in 1946 he has served as Chairman of the Council on Postgraduate Medical Education of the College, and during the 12 years intervening has the unique record of having organized and participated in 54 Postgraduate Courses in 14 cities with 3,704 physicians in attendance.

Dr. Peabody's interest in medical education began as Instructor of Medicine in 1921 at Georgetown University School of Medicine and later as Professor of Diseases of the Respiratory System. In 1951 he was awarded the Vicennial Medal for long and distinguished service. He was elected Emeritus Professor in 1957—marking 36 years of continuous teaching in the University. He is an alumnus member of Alpha Omega Alpha Honor Medical Society, Georgetown University.

As Superintendent of the Tuberculosis Hospital (1921-1934), Washington, D.C., and later as Medical Director of the new modern institution at Glenn Dale, Maryland, Dr. Peabody has constantly worked toward better care for the tuberculous patients in the District of Columbia. In 1953 he was awarded a certificate of merit by the Department of Public Health for 37 years of efficient service.

Dr. Peabody has been actively identified with the District of Columbia Tuberculosis Association since 1921—serving as President 1939-1943. He has been a member of the Board of Directors of the National Tuberculosis Association for many years, and is presently a member of the Advisory Council, American Trudeau Society.

He served as first Chairman of the Section on Diseases of the Chest, American Medical Association, which was organized in 1952 and is presently the Alternate Delegate from the Section to the House of Delegates of the American Medical Association. He is an Associate Editor of the journal, *Diseases of the Chest*, author of many editorials and papers on diseases of the chest and a contributor to several textbooks.

Dr. Peabody is a Diplomate of the American Board of Internal Medicine, and holds membership in many local, national, and international medical societies. He serves as Civilian Consultant in Diseases of the Chest at the U. S. National Naval Medical Center, Bethesda, Maryland and Glenn Dale, Maryland.

Donald R. McKay, M.D.

President
1958-1959

DR. DONALD R. McKAY

Takes Office as College President

Dr. McKay, Buffalo, New York, was born on February 22, 1898 in Sunnidale, Ontario, Canada. He graduated from the University of Toronto, Faculty of Medicine in 1925. Internship was served at the Buffalo City Hospital, later called the E. J. Meyer Memorial Hospital in Buffalo, New York. The following year was spent on the Obstetrics and Gynecology service before he decided on a medical career. He served as Assistant Resident in Medicine and later Resident in Medicine on the Tuberculosis Service of the E. J. Meyer Memorial Hospital and is presently Chief Attending Physician on this service. Since this Hospital is one of the teaching facilities of the University of Buffalo Medical School, he early became a member of the teaching staff, and presently is an Associate Clinical Professor of Medicine.

Other hospital affiliations include Attending Physician at the Millard Fillmore Hospital, another affiliate of the University of Buffalo Medical School and Consultant Physician at several other Western New York area hospitals, including the Veterans Administration Hospital in Buffalo and the New York State Hospital at Gowanda.

He has been a member of the American College of Chest Physicians since the formation of the New York State Chapter in 1941, serving as Secretary-Treasurer of the Chapter for four years. Later he became Regent of the College for New York, Regent at Large, Chairman of the Board of Regents and member of the Executive Council. He was elected Vice President in 1955.

Other medical associations include Fellowship in the American Medical Association, the New York State Medical Society, the Erie County Medical Society, a life member of the American College of Physicians, a member of the Trudeau Society, the New York State Society of Internal Medicine, the American Heart Association, the American Public Health Association and the Buffalo Academy of Medicine.

He has been a director of the Buffalo and Erie County Tuberculosis Association for nearly twenty years and President of the organization for the past five years. He is a director at large of the New York State Committee of Tuberculosis and Public Health. He is a past president of the Millard Fillmore Hospital Medical Staff, the E. J. Meyer Memorial Hospital Medical Staff and the Buffalo Academy of Medicine.

He has written or collaborated in writing several papers relating to pulmonary diseases.

Other interests include membership in several civic and fraternal organizations.

Dr. McKay and his wife Jessie G. reside in Eggertsville, New York, a suburb of Buffalo.

College Chapter News

MINNESOTA CHAPTER

The Minnesota Chapter will hold its annual meeting at Pine Beach Hotel on beautiful Gull Lake, Brainerd, Minnesota, Labor Day weekend. All College members and their families are invited. In addition to the interesting scientific program there will be bathing, water skiing, fishing, golf, horseback riding and special events for children. Write directly to the hotel for further information and reservations.

NEW CHAPTER OFFICERS

ARIZONA CHAPTER

President:	William B. Steen, Tucson
Vice-President:	Lloyd K. Swasey, Phoenix
Secretary-Treasurer:	Bertram L. Snyder, Phoenix

ILLINOIS CHAPTER

President:	Robert T. Fox, Evanston
President-Elect:	George H. Vernon, Edwardsville
Vice-President:	Gordon L. Snider, Chicago
Secretary-Treasurer:	Samson D. Entin, Chicago

MISSISSIPPI CHAPTER

President:	Thurman T. Justice, Jr., Gulfport
Vice-President:	Robert Neil Brown, Jackson
Secretary-Treasurer:	Lee R. Reid, Jackson

NEW JERSEY CHAPTER

President:	Lewis Baum, South Orange
President-Elect:	Arthur Bernstein, Newark
Vice-President:	A. A. Carabelli, Trenton
Secretary-Treasurer:	Emanuel Klosk, Newark

NEW YORK STATE CHAPTER

President:	Emil A. Naclerio, New York City
1st Vice-President:	Henry W. Leetch, Saranac Lake
2nd Vice-President:	Willard J. Davies, Rockville Center
Secretary-Treasurer:	Harry Golembe, Liberty (re-elected)

PHILIPPINE CHAPTER

President:	Jose Celis, Quezon City
President-Elect:	Manuel Quisumbing, Sr., San Pablo City
Vice-President:	Alejandro Sanchez Gaerlan, Manila
Secretary:	Priscilla J. Tablan, Quezon City (re-elected)

SOUTHERN CHAPTER OF SOUTH AFRICA

President:	David P. Marais, Cape Town
Vice-President:	Theodore Schrire, Cape Town
Secretary:	Hendrik Muller, Cape Town
Treasurer:	Michael J. Bailey, Cape Town

ERRATUM

We wish to call your attention to an error which appeared on page 420 in the April issue in a paper entitled "The Occurrence of Arrhythmias in Acute Myocardial Infarctions." The paper contained the statement "The authors believe that both digitalis and quinidine are contraindicated in the presence of complete heart block" which should have read "The authors believe that quinidine is contraindicated in the presence of complete heart block."

MEDICAL SERVICE BUREAU

POSITIONS WANTED

Chest physician, F.C.C.P., age 43, 16 years experience (staff physician, consultant, medical director) graduate Class A university, licensed Illinois, Michigan, seeks position in chest hospital. Please address inquiries to Box 298B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

F.C.C.P., F.A.C.S., residency-trained thoracic specialist seeks directorship of small chest hospital or chest service unit in teaching institution. Background includes 10 years full-time director chest surgical and bronchoscopic departments in large county hospital; broad administrative experience in hospital and industrial practice. Available September 1, 1958. Please address inquiries to Box 301B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

POSITIONS AVAILABLE

Assistant medical director wanted for 110-bed tuberculosis hospital. Salary $9,000 per year plus complete family maintenance including apartment, food, laundry, and utilities. Apply Executive Director, State Tuberculosis Hospital Commission, New Capitol Annex, Frankfort, Kentucky.

Physician wanted for moderate sized chest disease hospital. Residency training in pulmonary diseases. Man, 28-40 years, single. Graduate approved school—one year intership at least. Maintenance. State salary. Write Will Rogers Memorial Hospital, Saranac Lake, New York.

CALENDAR OF EVENTS

INTERNATIONAL MEETING

Fifth International Congress on Diseases of the Chest
Council on International Affairs
American College of Chest Physicians
Tokyo, Japan, September 7-11, 1958

CHAPTER MEETING

Colorado Chapter, Colorado Springs, September 28
Minnesota Chapter, Brainerd, August 30, 31, September 1

ANNOUNCEMENTS

Mr. Charles J. Haines, President of National Cylinder Gas Company of Chicago, has announced a change in that company's name to Chemetron Corporation.

Bennett Respiration Products, Inc. has introduced a new flow-sensitive resuscitator, designed for clinical administration of IPPB in therapy, resuscitation, or respiratory assistance, called the Bennett PR-1A Respiration Unit.

The University of Illinois College of Medicine, Department of Otolaryngology, Chicago, announces its Annual Otolaryngologic Assembly, consisting of intensive lectures and panels on advancements in otolaryngology, will be held September 29 - October 5, 1958. For information, please write to the Department of Otolargynology, 1853 West Polk Street, Chicago 12, Illinois.

The Department of Laryngology and Bronchoesophagology, Temple University Medical Center, Philadelphia, will present a Postgraduate Course in Bronchoesophagology November 3-14, 1958 under the direction of Drs. Chevalier L. Jackson and Charles M. Norris. Information and application forms may be obtained from Dr. Chevalier L. Jackson, 3401 North Broad Street, Philadelphia 40, Pennsylvania.